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Backg d

Hypertension in pregnancy stand alone or with proteinuria is one of the leading causes of maternal mortality and morbidity in the world [1]. Hypertensive disorders are the second most common cause of maternal deaths worldwide [2] and account for more than 40,000 maternal deaths annually [3]. These disorders are also associated with adverse perinatal outcomes such as stillbirth, preterm and small for gestational age babies [4-6].

Epidemiological and clinical studies have shown that an inverse relationship exists between calcium intake and development of hypertension in pregnancy [4,7]. Many trials have been conducted to observe the protective effect of preventive calcium supplementation in pregnant women [8]. There is substantial data that supports that calcium supplementation in pregnancy is associated with reduction in gestational hypertensive disorder [9,10], although the impact varies according to the baseline calcium intake of the population and pre-existing risk factors [8,11].

A previous review by Hofmyer et al. has shown that calcium supplementation during pregnancy had a significant effect in reducing risk of gestational hypertension and pre-eclampsia [10]. This effect was more prominent in those studies where participants had low baseline calcium intake compared to that of adequate calcium intake [10]. Another review by Trumbo et al. had shown that beneficial effects of calcium supplementation cannot be generalized to USA population and suggested that beneficial effects could only be shown in populations whose baseline calcium intake is inadequate [11].

The objective of this review was to evaluate the effect of calcium supplementation during pregnancy in reducing maternal hypertensive disorders and related maternal and neonatal mortality and morbidity in developing countries. This paper is a part of series of papers for Lives Saved Tool (LiST) model. An intervention is currently included in the LiST if there is substantial evidence that it decrease maternal mortality, neonatal/child mortality and/or stillbirths [12]. This process is guided by qualitative assessment of available evidence according

All the included trials were assessed for methodological quality and outcomes of interest using a standardized form [12]. Data were abstracted for study design, study site, methods of sequence generation, allocation concealment, attrition and primary outcomes of interest. Individual studies were evaluated according to CHERG adaptation of GRADE technique [12,13]. In this method of qualitative evaluation, all RCTs received an initial score of 'high' and an observational study as 'low'. The study scores were adjusted depending on limitations of the study design. Trials with a final grade of 'high' or 'moderate' and 'low grade' were included in the analysis with exclusion of studies with a final grade of 'very low' [12].

The primary outcomes assessed were maternal mortality, gestational hypertension (± proteinuria), pre-eclampsia, severe pre-eclampsia and eclampsia. Data on neonatal outcomes like neonatal mortality, preterm birth, low birth weight and birth of small-for-gestational age were also extracted. Pooled analyses were conducted where data were available from more than one study for an outcome. The results are presented as risk ratios (RR) and 95% confidence intervals (CIs). The assessment of statistical heterogeneity among trials was done by visual inspection i.e. the overlap of the confidence intervals among the studies, and by the Chi square (P-value) of heterogeneity in the meta-analyses. A low P value (less than 0.10) or a large chi-squared statistic relative to its degree of freedom was considered as providing evidence of heterogeneity. The I^2 values were also looked into and I^2 values greater than 50% were taken as substantial and high heterogeneity. In situations of substantial or high heterogeneity being present, causes were explored by sensitivity analysis and random effects model were used. Although random model is not a substitute for a thorough investigation of heterogeneity, it takes an 'average' effect from all the included studies compared to fixed models that take the exact contribution from the individual studies [16].It is thus preferred in case of significant heterogeneity in pooled estimate. All analyses were conducted using software Rev Man version 5 [17]. We did a subgroup analysis based on a priori hypothesis that calcium supplementation during pregnancy would be more effective in reducing hypertensive disorders in pregnant women who are at increased risk for developing gestational hypertensive disorders. Participants were defined as being at a higher risk of developing hypertension in pregnancy in case of teenage pregnancy, women with previous pre-eclampsia, and women with positive roll over test and/or positive angiotension II sensitivity test [10]. We applied CHERG rules to collective maternal and neonatal mortality and morbidity outcomes related to maternal hypertensive disorders [12]. The purpose of this exercise was to get a point estimate for effectiveness of calcium supplementation during pregnancy in reducing maternal and neonatal mortality due to hypertensive disorders.

Re l

Literature search of electronic databases, and papers from hand searches yielded a total number of 1402 titles after removal of duplicates (Figure 1). Initially 29 studies were considered for inclusion in the review. Out of these seven studies were excluded due to insufficient data on outcomes of interest [18-24]. Three studies were excluded due to very low grade quality [25-27]. In two trials, calcium was supplemented as therapeutic intervention and not as preventive [28,29]. Two studies were excluded because calcium was supplemented in combination, either with linoleic acid [30] or L-aspartate [31] and it was not possible to separate out their effect from calcium supplementation. Five studies were excluded because they were conducted in developed countries [32-36].Finally 10 studies that met our inclusion criteria were included in the review [37-46].

All the included studies were randomized controlled trials with comparison group receiving a placebo in all except in two studies in which participants of comparison group were simply observed as controls [45,46]. Table 1 presents characteristics of included studies. The starting period of calcium supplementation in all the included studies was before 20-32 weeks of gestation and continued till delivery. In three of the included studies [39,40,42], the participants were defined as being at a higher risk of developing hypertension in pregnancy (pregnant teenage girls, women with previous pre-eclampsia or women with positive roll over test). The dose of calcium ranged from 0.5 g/day to 2 g/day. Five of the included studies were from Asia [38,42,43,45,46] and four from South America [37,39-41]. One large multicentre trial was conducted by World Health Orga-

The overall quality grade for this outcome was that of ‘low’

Table 1 Cha ac e i ic f i cl ded die

of calcium group and 25 cases in 4161 participants of control group giving a relative risk of 0.68 (95 % CI 0.48-0.97). A quality grade of 'low' was assigned due to low number (<50 events) of events in the intervention and control group.

Severe pre-eclampsia

The outcome of severe pre-eclampsia was reported by three included trials [44-46] with a 30% reduction in calcium group compared to control, however the results were not statistically significant [(RR 0.70; 95% CI 0.46-1.05) (Figure 2). There were a total of 4531 participants in calcium group and 4541 participants in control group. There was no heterogeneity in the pooled data. The overall quality grade for this estimate was that of 'moderate' level due to lack of placebo in two studies and confidence interval including unity. We did not perform any subgroup analysis for this outcome due to fewer numbers of studies reporting this outcome.

Pre-eclampsia

The impact of calcium supplementation during pregnancy on risk of pre-eclampsia was reported in 10 studies [37-46]. The analysis comprising 5697 women in intervention group and 5708 women in control group showed a reduction of 59% [RR 0.41; 95 % CI 0.24-0.69, random model] in the intervention group compared to control (Figure 3). On visual inspection of the forest plot, five of the included studies were showing a clear benefit. There was a substantial heterogeneity in the pooled data (I^2=74), so the random models were used. The reduction was more marked in participants with a higher pre-pregnancy risk of developing gestational hypertensive disorders [RR 0.18, 95 % CI 0.07-0.42, random model] compared to that of low risk women [RR 0.51, 95 % CI 0.30-0.87]. The overall quality grade for reduction in risk of pre-eclampsia was that of 'High' level.

Taherian 2002	3
Villar 2006	35
Wanchu 2001	0
(%	
Total events	38

Heterogeneity: Chi² = 0.98, df = 2 (P = 0.61); I² = 0%

Test for overall effect: Z = 1.74 (P = 0.08)

Gestational hypertension (± proteinuria)

The effect of calcium supplementation on gestational hypertension (± proteinuria) was assessed in six studies from developing countries [37,40-44]. A random effect model pooled analysis showed a significant reduction of 45 % in risk of development of gestational hypertension in women receiving calcium supplementation (4919 women in calcium group) as compared to those receiving control (4942 women in control group) [RR 0.55; 95 % CI 0.36-0.85] .On visual inspection of forest plot, four of the included studies were showing a clear benefit in favor of intervention (Figure 4). There was a significant heterogeneity in the pooled data (I^2=82%) and the random models were used. The overall grade quality for this estimate was that of 'High' level. Women who were at higher risk of development of hypertension

during pregnancy seems to have a more prominent preventive effect of calcium supplementation [RR 0.32, 95 % CI 0.06-1.63] compared to those at lower risk [RR 0.64, 95 % CI 0.39-1.05], however the results were not statistically significant for both the subgroups (Figure 4).

Neonatal outcomes

One study reported effect of calcium supplementation during pregnancy on neonatal mortality [44]. There was a significant reduction of 30 % in the intervention group compared to placebo (RR 0.70; 95 % CI 0.56-0.88). Data on preterm births were included from five trials [37,38,40,43,44] and the pooled analysis showed a significant reduction of 12% (RR 0.88; 95% CI 0.78-0.99) in the intervention group compared to control (Figure 5). The overall grade for this estimate was that of 'high level'.

number of events being less than 50 (Rule 1) [12]. Therefore, severe morbidity outcomes were considered. Considering the direction of effect, value of effect size and statistical significance of the estimates, reduction in severe maternal morbidity/mortality was chosen for inclusion in the LiST (Rule 3).This combined outcome was reported by one study and included severe gestational hypertensive related morbidities that can lead to maternal mortality [44]. The qualitative assessment of this estimate was that of 'moderate' level however downgraded to 'low' to translate it to maternal mortality[47].

To estimate the effectiveness of calcium supplementation during pregnancy on neonatal outcomes, CHERG rules were applied to the outcomes of neonatal mortality, preterm birth, and small for gestational age and low birth weight. One study reported all-cause neonatal mortality which showed significant reduction of 30 % with 37 events in the intervention and 53 events in control group [44]. The overall quality grade for this estimate was that of moderate level which was also downgraded to 'low' for translating all-cause into cause

intake [11]. This conclusion was based on critical evaluation of studies conducted in similar setting as that of USA; however no meta-analysis was performed.

Our results are confirmatory for the above mentioned reviews. If we pool all the studies from both developed and developing countries, the estimates become RR 0.70 (95 % CI 0.57-0.86) for gestational hypertension, RR 0.47 (95 % CI 0.34-0.66) for pre-eclampsia and RR 0.76 (95 % CI 0.59-0.97) for risk of preterm birth. Estimates for gestational hypertension and pre-eclampsia are similar to that of Hofmyer et al. [10] however the results for risk of preterm birth became statistically significant. This is due to addition of new study from India by Kumar et al which had shown a significant effect in reduction in risk of preterm birth [38]. When we separately pooled the results of studies from developed countries only [32-36], the estimate came to be RR 0.77 (95% CI 0.57, 1.03, random model) for gestational hypertension, RR 0.52 (95 % CI 0.27, 1.00, random model) for pre-eclampsia and RR 0.63 (95 % CI 0.33, 1.19, random model) for preterm birth (data not shown).This shows that calcium supplementation did not have any significant effect on risk of gestational hypertensive disorders in developed countries as is shown in the descriptive review of FDA [11].

What could be the explanation of protective effect of calcium supplementation during pregnancy in developing countries and no effect in developed countries? The first and the foremost is the difference in baseline

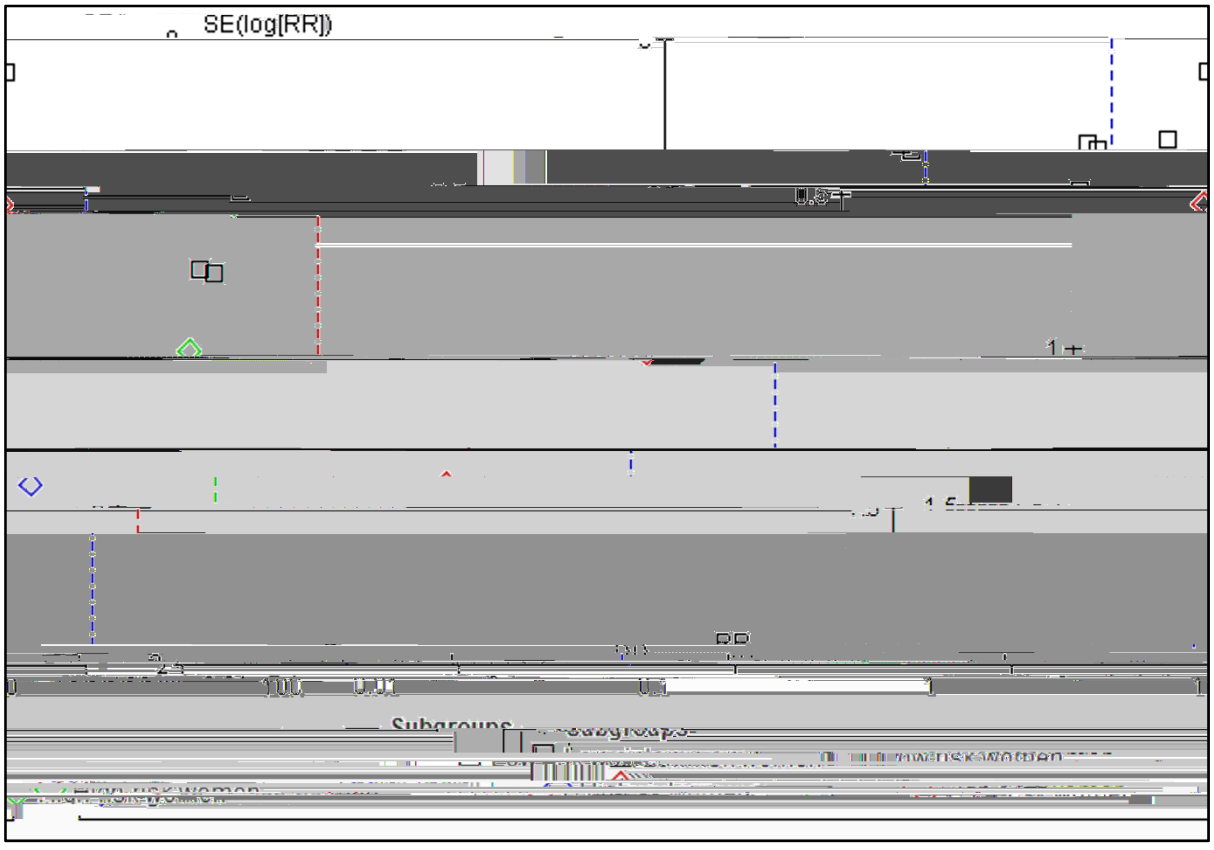

Fig e 7 .

severe morbidities (Additional File 1). It is important to note that maternal calcium supplementation during pregnancy is not only effective in reducing neonatal mortality but also morbidities later in childhood. A review by Bergel and Barros had reported that offspring of women who were supplemented with calcium during pregnancy had low incidence of hypertension in childhood [52].

Our review has certain limitations. In two of the included studies [45,46], the comparison group did not receive the placebo but the participants were simply observed as controls. This could have biased the results in favor of intervention [16]. We did not look at the side effects related to calcium supplementation during pregnancy. The previous reviews, however, have shown that it is not associated with any particular harmful effects [10].

Findings of this review and those of previous reviews gave conclusive evidence on effectiveness of calcium supplementation during pregnancy in reducing maternal gestational hypertensive related disorders in populations with low baseline calcium intake [8,11]. Future research should focus on delivery platforms, regimens and programmatic aspect of the intervention. It would be relevant to assess the bioavailability of calcium when delivered for example via dietary modification or food fortification. It is important for example to determine effectiveness of calcium supplementation by dietary modification at places where baseline calcium intake is from dairy products compared with those where it is mostly taken in from vegetarian sources. It is also important to calculate an internationally accepted value to define adequacy given the large variations in calcium recommendations in different countries of the world.

Implementation of recommendation of calcium supplementation to all pregnant women in developing countries poses a major challenge to policy-makers and program managers of these countries. It is important to take steps for procurement of the preparation, storage, distribution, quality-control, and compliance assurance with daily supplements to large numbers of pregnant women. It is also important to consider cultural, financial, and educational barriers to changing policy and lessons should be learnt from practices of previous programs like iron+folic acid supplementation schemes in these countries. Lack of infrastructure and

poor compliance were considered as few of the major barriers in implementation of these programs in these countries [53]. Issues of cost effectiveness should also be considered and weighed for increasing the calcium intake by dietary modification or food fortification. Increasing dietary calcium intake may seem to be an easier intervention than calcium supplementation, although availability of dairy products in many coun-