

REVIEW

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# Quantifying the fall in mortality associated with interventions related to hypertensive diseases of pregnancy

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## Abstract

**Background:** The burden of hypertensive diseases of pregnancy (HDP) is high, and the associated mortality is substantial. The aim of this study was to quantify the fall in mortality associated with interventions related to HDP.

**Methods:** We conducted a systematic review of the literature to identify studies that reported the mortality associated with HDP. We used a meta-analysis to estimate the relative risk of mortality associated with HDP. We also estimated the relative risk of mortality associated with interventions related to HDP.

**Results:** We identified 10 studies that reported the mortality associated with HDP. The relative risk of mortality associated with HDP was 1.5 (95% CI 1.2-1.8). The relative risk of mortality associated with interventions related to HDP was 0.7 (95% CI 0.5-1.0).

**Conclusions:** The burden of HDP is high, and the associated mortality is substantial. Interventions related to HDP can reduce the mortality associated with HDP.

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## Introduction

The fifth Millennium Development Goal has set targets for the reduction of maternal mortality by 2015, but progress has been slow [1,2]. Effective interventions to reduce maternal deaths exist but they are often not available to women in poor countries [3]. Where resources are limited, information on the costs and health effects of interventions is thought to be important to aid decisions on how to reach the MDG-goals [4]. Such information may help to determine what can be achieved with existing resources, and to decide how additional funds can be used to maximise the chances of achieving the MDG-goals [4].

WHO estimates that 88 to 98 percent of maternal deaths are avoidable with moderate levels of health care [5]. This deceptively simple statement hides the complexities underlying the assessment of the health effects of interventions [6]. First, evidence of the efficacy of interventions needs to be available. In maternal health, reliable evidence of an effect on maternal mortality is rarely available and reliance on lower quality evidence – by current scientific standards - is often necessary [3]. Second, a distinction needs to be made between efficacy and effectiveness. Effectiveness, taking into account the coverage and quality of service delivery is thought to be more representative of the real world, but it requires robust evidence from a large range of programme settings. Third, interventions act on disease incidence,

Population models quantifying the impact of the  
intervention treatment of HDP on mortality from HDP at  
the population level

We searched PubMed for articles quantifying the impact of  
maternal health interventions on the reduction of maternal  
mortality at the population level, using the terms interven-  
tions, maternal mortality and effectiveness in our search.  
Reference lists from all relevant articles were checked. We  
included articles reporting the effect of preventive or cura-  
tive interventions on HDP-related mortality, regardless of  
the definitions used. Information was extracted on inter-  
ventions, the health systems level at which the intervention  
was delivered, the mortality outcome, the reported risk  
reduction on mortality outcomes, the methods for estimat-

routine calcium supplementation in pregnancy [40] and antiplatelet agents during pregnancy in women at risk of pre-eclampsia [41] and three treatment interventions: Magnesium sulphate (MgSO4) for the treatment of eclampsia (3 reviews) [42-44] MgSO4 for the treatment of pre-eclampsia [45], and hypertensive drugs for the treatment of mild to moderate hypertension in pregnancy [46]. The review documenting the effect of oral beta-blockers for hypertension [47] is not reported separately because beta-blockers are included in a later review of hypertensive drugs [46]. All studies are randomized controlled trials, and the quality of the trials is generally high. The number of deaths reported was sufficient in only one review [42] and one review combined death with severe morbidity to increase the number of adverse events [40].

There is no doubt that treating women with eclampsia with MgSO4 reduces the risk of maternal death compared to diazepam (RR 0.59 95% CI 0.37-0.94), though the effect against placebo is not known. MgSO4 is also effective for the treatment of pre-eclampsia: treating women with pre-eclampsia with MgSO4 reduces their risk of eclampsia (RR 0.41 95% CI 0.29-0.58) and placental abruption (RR 0.64 95% CI 0.50-0.83), though there is insufficient evidence to draw conclusions with regard to the risk of death. The efficacy of the treatment of hypertension in pregnancy is less clear. Antihypertensive drugs in women with mild to moderate hypertension do not lower the risk of pre-eclampsia and there are insufficient numbers of events to assess their effect on risk of eclampsia or maternal death. Antihypertensive drugs do halve the risk of developing severe hypertension (RR 0.50 95% CI 0.41-0.61) [46].

Routine calcium supplementation during pregnancy halves the risk of pre-eclampsia (RR 0.45 95% CI 0.31-0.65), and reduces the occurrence of a composite outcome of death or serious morbidity (RR 0.80 95% CI 0.65-0.97). The reduction in the risk of pre-eclampsia is greatest for women at high risk of pre-eclampsia (5 trials, 587 women: RR 0.22, 95% CI 0.12-0.42), and for those with low baseline calcium intake (8 trials, 10,678 women: RR 0.36, 95% CI 0.20-0.65). There is a 17% reduction in the risk of pre-eclampsia with the use of antiplatelet agents – mostly low dose aspirin - during pregnancy in women at risk of pre-eclampsia (RR 0.83 95% CI 0.77-0.89). However, there are no significant differences between antiplatelet agents and placebo in the risk of eclampsia or maternal death.

**Population models** – analyzing the impact of the intervention on the occurrence of HDP on mortality from HDP at the population level

We found 15 studies quantifying the effect of maternal health interventions on reducing maternal mortality at

the population level, ten of which are included here (Additional File 2). Five studies were excluded because they did not report on HDP specifically [48-51] or because findings were only presented in a chart with no information on assumptions or the data underlying the chart [52].

The approach to classifying interventions varies greatly (Additional File 2). Most authors include a health systems dimension aimed at separating interventions that can be delivered at the primary or health centre level from those that require hospital treatment, though definitions are rarely provided and there is no consistency in the types of interventions that are deemed effective at the various levels. At the hospital level, effective interventions usually consist of MgSO4 for the treatment of eclampsia [53-59], and later studies also include MgSO4 for the treatment of pre-eclampsia. [55,58-60] Caesarean section is generally listed as part of the hospital package, and Graham et al (2006) [55] also include calcium supplementation, low dose aspirin, antioxidants and antihypertensive drugs as effective interventions at the hospital level.

Primary care interventions tend to focus on screening on: -11(ea)--2





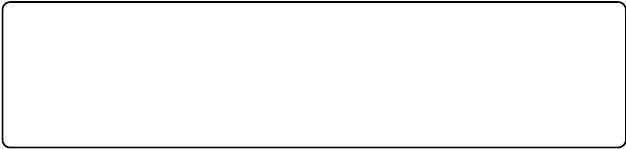


eclampsia. [80] Treatment of severe hypertension is essential, but the choice of drug is not obvious, and an experienced clinician needs to decide on a case by case basis [46]. MgSO<sub>4</sub> has been suggested for use at the primary care level, but MgSO<sub>4</sub> is difficult to administer, and health centres need to refer women to hospital, even if they are able to give a loading dose.

Table 4 suggests potential effect estimates for the reduction of HDP related mortality based on this review. We postulate that health centres without access to referral care can contribute to a 20% reduction in death from HDP



with qualified staff and drugs, much greater reductions can



Pridone (vitamin B6) supplementation in pregnancy. *Cochrane Database of Systematic Reviews* Issue 2, Art. No.:CD000179.

Oestrogen supplementation, mainly diethylstilbestrol, for preventing miscarriages and other adverse pregnancy outcomes. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD004353.

Progesterone for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD006175.

Marine oil, and other prostanoid precursors, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD003402.

Garlic for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD006065.

Diuretics for preventing pre-eclampsia. *Cochrane Database of Systematic Reviews* Issue 1, Art. No.:CD004451.

Nitric oxide for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* Issue 2, Art. No.:CD006490.

Energy and protein intake in pregnancy. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD00032.

Altered dietary salt for preventing pre-eclampsia, and its complications. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD005548.

Reduced salt intake compared to normal dietary salt, or high intake, in pregnancy. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD001687.

Exercise or other physical activity for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* Issue 2, Art. No.:CD005942.

Bed rest with or without hospitalisation for hypertension during pregnancy. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD003514.

Low-dose dopamine for women with severe pre-eclampsia. *Cochrane Database of Systematic Reviews* Issue 1, Art. No.:CD003515.

Plasma volume expansion for treatment of pre-eclampsia. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD001805.

Interventionist versus expectant care for severe pre-eclampsia before term. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD003106.

Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD001449.

Rest during pregnancy for preventing pre-eclampsia and its complications in women with normal blood pressure. *Cochrane Database of Systematic Reviews* Issue 2, Art. No.:CD005939.

Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *International Journal of Gynaecology and Obstetrics* 105.

Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 374.

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD001059 (updated 1 February 2010).

Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database of Systematic Reviews* Issue 2, Art. No.:CD004659.

Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database of Systematic Reviews* Issue 4, Art. No.:CD000127.

Magnesium sulphate versus phenytoin for women with eclampsia. *Lancet* 374.

Magnesium sulphate versus lidocaine cocktail for eclampsia. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD002960.

Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Lancet* 374.

Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews* Issue 1, Art. No.:CD002252.

Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews* Issue 3, Art. No.:CD002863.

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Saving maternal lives in resource-poor settings: facing reality. *Health Affairs* 89.

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Eclampsia in the United Kingdom 2005. *BJOG* 114.

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