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## Postpartum management of hypertensive disorders of pregnancy: a systematic review

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# 1 Postpartum management of hypertensive disorders of 2 pregnancy: a systematic review

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21 **Short title:** Postnatal Hypertension Management

22 **Competing interests statement:** None of the authors has any conflicts of interest to declare.

## 23 **Abstract**

### 24 **Objectives**

25 Hypertensive disorders of pregnancy (HDP) affect one in ten pregnancies and often persist  
26 postpartum when complications can occur. We aimed to determine the effectiveness and  
27 safety of pharmacologic interventions, other interventions, and different care models for  
28 postpartum hypertension management.

### 29 **Design**

30 A systematic review was undertaken. Nine electronic databases, including Medline, were  
31 searched from inception to 16/03/2017. After duplicate removal, 4,561 records were  
32 screened. Two authors independently selected studies, extracted study characteristics and  
33 data, and assessed methodological quality.

### 34 **Setting**

35 Randomised controlled trials, case-control studies, and cohort studies from any country and  
36 healthcare setting.

### 37 **Participants**

38 Postnatal women with HDP.

### 39 **Interventions**

40 Therapeutic intervention for management of hypertension, compared with another  
41 intervention, placebo, or no intervention.

### 42 **Primary and secondary outcome measures**

43 Outcome data were collected for maternal mortality and severe morbidity; systolic, diastolic  
44 and mean arterial blood pressure (BP) control; and safety data. Secondary outcome data  
45 collected included the length of postnatal hospital stay and laboratory values.

### 46 **Results**

47 39 studies were included (n=2,901). Results were heterogeneous in terms of intervention,  
48 comparison and outcome requiring a narrative approach. There were insufficient data to  
49 recommend any single pharmacologic intervention. 18 studies reported calcium-channel  
50 blockers, vasodilators and beta-blockers lowered BP postpartum. 12 of these reported safety  
51 data. Limited data existed regarding management in the weeks following hospital discharge.  
52 Neither loop diuretics (three studies) nor corticosteroids (one study) produced clinical benefit.

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3 53 Uterine curettage significantly reduced BP over the first 48 hours postpartum (range 6-  
4 54 13mmHg) compared to standard care (eight studies), with safety data only reported by 4/8  
5 55 studies.  
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## 8 56 **Conclusion**

9  
10 57 There was insufficient evidence to recommend a particular BP threshold, agent, or model of  
11 58 care but three classes of antihypertensive appeared variably effective. Further comparative  
12 59 research, including robust safety data, is required. Curettage reduced BP, but without  
13 60 adequate reporting of harms, so cannot currently be recommended.  
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## 18 61 **Strengths and limitations of this study**

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20  
21 62 • All types of intervention for the management of postpartum hypertension – medical,  
22 63 surgical and organisation of care – were eligible for inclusion in this review.  
23  
24 64 • Randomised controlled studies plus other experimental study designs (cohort studies,  
25 65 case-control studies and quasi-randomised studies) were included and no limitations  
26 66 were imposed in terms of language or publication date, resulting in a comprehensive  
27 67 review.  
28  
29 68 • This review highlights significant evidence gaps, demonstrating that further  
30 69 comparative research is required, particularly to clarify postpartum antihypertensive  
31 70 selection.  
32  
33 71 • Although 39 studies were included, the majority had a high risk of bias such that the  
34 72 evidence provided by this review is of low quality.  
35  
36 73 • The 39 studies reported a broad range of heterogeneous outcomes, limiting  
37 74 meaningful comparison.  
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## 47 75 **Keywords**

48  
49 76 Preeclampsia, gestational hypertension, postpartum, hypertensive disorders of pregnancy,  
50 77 antihypertensive medication, systematic review  
51  
52

## 53 78 **Abbreviations**

54  
55 79 BP Blood pressure  
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3 80 HDP Hypertensive disorders of pregnancy  
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5 81 MAP Mean arterial pressure  
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8 82 NICE National Institute of Health and Care Excellence  
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10 83 RCT Randomised controlled trial  
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13 84 SSRI Selective serotonin reuptake inhibitor  
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## 86 **Introduction**

87 Hypertensive disorders of pregnancy (HDP) often persist following delivery,<sup>1</sup> and  
88 occasionally arise de novo postpartum.<sup>2</sup> In both scenarios adverse events can occur during  
89 this period. Approximately one-third of eclampsia occurs postpartum, nearly half beyond 48  
90 hours after childbirth.<sup>3-5</sup> Half of the women who sustain an intracerebral haemorrhage in  
91 association with preeclampsia do so following birth.<sup>6</sup> Women may enter the postnatal period  
92 requiring large doses of antihypertensive medication, but the majority will be treatment-free  
93 by three to six months.<sup>1 7</sup> This rapidly changing blood pressure (BP) poses a challenge in  
94 terms of appropriate antihypertensive selection and dose adjustment.

95 The National Institute for Health and Care Excellence (NICE) recommends frequent  
96 postnatal BP monitoring for women with both preeclampsia (every one to two days for two  
97 weeks) and gestational hypertension (at least once between day three and five).<sup>8</sup> The  
98 guideline stipulates thresholds for the increase or commencement ( $\geq 150/100$ mmHg) and the  
99 reduction or cessation (consider  $< 140/90$ mmHg and reduce  $< 130/80$ mmHg) of  
100 antihypertensive medication after birth. However, little detail is provided about frequency or  
101 proportion of dose reduction or how to manage multiple medications.<sup>8</sup> The American College  
102 of Obstetricians and Gynecologists recommend that BP be monitored in hospital (or with an  
103 equivalent level of outpatient surveillance) for 72 hours after birth, and checked again seven  
104 to ten days postpartum (sooner if a woman is symptomatic).<sup>9</sup> In line with NICE, they propose  
105 treating BP when  $\geq 150/100$ mmHg, but add this should be on two measures, four to six hours  
106 apart. They make no suggestion regarding BP thresholds for medication reduction, implying  
107 uncertainty about when to decrease or stop treatment.

108 A Cochrane review (search date January 2013) evaluated medical interventions for  
109 prevention and treatment of postnatal hypertension. This was limited to randomised  
110 controlled trials (RCTs) and included only nine studies.<sup>10</sup> Given the paucity of evidence  
111 available, we have undertaken an updated systematic review of the postpartum management  
112 of hypertension in women with HDP with a broader scope: including the full range of  
113 interventions studied, and incorporating cohort and case-control studies, alongside RCTs. Our  
114 specific questions were: [1] How should BP be monitored in women with HDP postpartum?  
115 [2] What BP thresholds should be used for antihypertensive treatment initiation, adjustment  
116 and cessation postpartum? [3] Which antihypertensive medication(s) should be used in

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3 117 postpartum in women with HDP? [4] What are the benefits and harms of other therapeutic  
4 118 interventions for women with HDP postpartum?  
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### 8 **Material and methods**

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10 120 A protocol, with explicitly defined objectives, study selection criteria, and approaches to  
11 121 assessing study quality, outcomes and statistical methods, was developed (Appendix S1).  
12 122 This was registered with PROSPERO: International Prospective Register of Systematic  
13 123 Reviews (CRD42015015527) and is available online  
14 124 ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015015527](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527)). We  
15 125 followed the guidelines for meta-analyses and systematic reviews outlined by the Preferred  
16 126 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix  
17 127 S2).<sup>11</sup>  
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24 128 A systematic literature review was undertaken to capture evidence from human studies  
25 129 regarding postpartum hypertension management in women with HDP, without restriction by  
26 130 language or publication date (Appendix S1). We searched the following databases, from  
27 131 inception to 16/03/2017: Cochrane Database of Systematic Reviews (CDSR), Database of  
28 132 Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials  
29 133 (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL),  
30 134 Embase, Medline, PsycINFO, Science Citation Index, Science (Web of Science Core  
31 135 Collection), Social Science Citation Index & Conference Proceedings Citation Index. We  
32 136 hand-searched reference lists and contacted relevant experts for potentially relevant studies,  
33 137 which might have been missed by electronic searches.<sup>12</sup>  
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41 138 We included RCTs, quasi-randomised studies, case-control studies, prospective and  
42 139 retrospective cohort studies, assessing interventions for hypertension management  
43 140 postpartum in women with HDP (gestational hypertension, pre-eclampsia, chronic  
44 141 hypertension and super-imposed pre-eclampsia). Consistent with guidance from Cochrane,  
45 142 conference abstracts were included.<sup>5</sup>  
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50 143 Two reviewers (AC/LP) independently screened the titles and abstracts, and then critically  
51 144 reviewed the full text of selected studies to assess eligibility. Discrepancies were resolved by  
52 145 discussion before independent extraction of relevant data by the two reviewers. For trials with  
53 146 multiple intervention arms, we extracted data from eligible comparison arms. Data were  
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3 147 extracted for the primary and secondary outcomes outlined in Table 1. Due to the  
4 148 heterogeneous nature of these studies, a narrative synthesis was undertaken.

7 149 Two reviewers (AC/LP) independently assessed each trial's methodological quality using the  
8  
9 150 Cochrane Collaboration's tool for assessing the risk of bias in RCTs,<sup>13</sup> and the Newcastle-  
10 151 Ottawa scale for case-control and cohort studies.<sup>14</sup> A global assessment of bias across trials  
11  
12 152 was made.

## 153 **Results**

154 Our searches yielded 7,105 records and after excluding duplicates, 4,561 titles and abstracts  
155 were screened (Figure 1). 80 full-text articles were assessed: 35 articles were excluded  
156 (Appendix S3). 45 articles, representing 39 studies (32 randomised trials, two prospective  
157 cohort studies, and five retrospective cohort studies) reporting data from 2,901 postnatal  
158 participants met our inclusion criteria (Appendix S4). 9/39 (23%) were published only as  
159 conference abstracts. No further details were made available following author contact.

160 A range of interventions was assessed including antihypertensive medications (18 studies,  
161 n=982), loop diuretics (four studies, n=503), parenteral steroids (one study, n=157), other  
162 medications (six studies, n=188), uterine curettage (eight studies, n=837) and novel models of  
163 care (two studies, n=234). 9/39 (23%) included  $\geq 100$  participants, and only two studies  
164 included  $\geq 200$  participants.<sup>15 16</sup> Four were from lower-middle-income settings<sup>15 17-19</sup>  
165 (classified according to the United Nations<sup>20</sup>), and 13/39 (33%) studies had follow-up periods  
166 longer than seven days (Appendix S4). Only 5/39 (13%) and 7/39 (18%) studies,  
167 respectively, reported maternal mortality or major maternal morbidity, and whilst the  
168 majority of studies did report some measure of BP control, three did not (Tables 2a&b).  
169 19/39 (49%) studies reported safety data (Tables 2a&b).

170 5/39 (13%) studies (all evaluating antihypertensive medications) involved mixed antenatal  
171 and postnatal populations<sup>17 21-24</sup>. Authors were contacted to request their dataset for the  
172 postnatal participants, but no data were made available. 6/39 (15%) studies included  
173 participants with chronic hypertension alongside women with de novo HDP (gestational  
174 hypertension or pre-eclampsia).<sup>22 23 25-31</sup> 12/39 (31%) studies included women with eclampsia  
175 – in one all participants were eclamptic (Appendix S5).<sup>17</sup>

176 30/32 (94%) included RCTs were judged to be at high overall risk of bias, by both reviewers,  
177 according to the Cochrane tool, 23/32 (72%) for multiple domains. Only 2/32 (6%) were

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3 178 thought to be clearly at low risk of bias.<sup>29-32</sup> All included cohort studies were deemed to have  
4 179 a high risk of bias in at least one domain of the Newcastle-Ottawa scale (Appendix S6).

7 180 **How should blood pressure be monitored postpartum in women with hypertensive**  
8 181 **disorders of pregnancy?**

10 182 No studies specifically addressed the frequency or method of postnatal BP monitoring. Two  
11 183 evaluated the impact of postpartum care organisation (n=234), using the postnatal  
12 184 readmission rate as their primary outcome (Appendix S4). Neither reported maternal  
13 185 mortality or morbidity, safety data nor any measure of BP control (Table 2b).<sup>26 33</sup>

17 186 One assessed introduction of a specialised postpartum clinic (no further details were given)  
18 187 and demonstrated an increased postnatal readmission and triage visit rate (22% intervention  
19 188 group, 9% control group: difference 13%,  $p<0.04$ ) although 86% occurred before a  
20 189 participant was seen in the clinic.<sup>33</sup> The second study evaluated specialist nurse follow-up,  
21 190 including home visits and telephone contact, and reported no significant difference in the  
22 191 postnatal readmission rate compared to standard care.<sup>26</sup>

28 192 **What blood pressure thresholds should be used for antihypertensive treatment**  
29 193 **initiation, adjustment and cessation postpartum?**

30 194 No relevant studies identified.

34 195 **Which antihypertensive medication(s) should be used postpartum in women with**  
35 196 **hypertensive disorders of pregnancy?**

37 197 14 randomised trials (n=645), one quasi-randomised trial (n=15), and three retrospective  
38 198 cohort studies (n=322) evaluated antihypertensive medications (Appendix S4). Only three  
39 199 studies reported maternal mortality,<sup>29-31 34 35</sup> and three reported maternal morbidity: no  
40 200 differences between groups were reported (Table 2a).<sup>29-31 35 36</sup> 12 studies reported safety data,  
41 201 in comparisons between multiple classes of antihypertensive agents (Table 2a): no clear  
42 202 differences were established, although one study found a greater number of minor side effects  
43 203 reported with oral nifedipine than with oral labetalol.<sup>27 28</sup>

49 204 The vast majority of included studies evaluated either acute control of severe hypertension  
50 205 (7/18, 39%), or BP control in the few days after delivery, whilst women remained hospital  
51 206 inpatients (8/18, 44%). Only three studies, two published only as conference abstracts,  
52 207 evaluated BP control in the weeks and months following hospital discharge.<sup>25 27 28 37</sup>

### 208 **Calcium-channel blockers**

209 Three small studies examined oral nifedipine (n=135): nifedipine resulted in a greater  
210 decrease in MAP 18-24 hours after childbirth than placebo (intervention group  
211 93.9±1.6mmHg, control group 100.2±2.6mmHg, difference 6.3mmHg,  $p<0.05$ ), but not at  
212 other time points to 48 hours (one RCT, n=31).<sup>32</sup> Nifedipine controlled severe hypertension  
213 to <160/100mmHg more quickly than labetalol (intervention group 25.1±13.6 minutes,  
214 control group 43.6±25.4 minutes: difference 18.5 minutes,  $p=0.002$ ; one RCT, n=21).<sup>21</sup> A  
215 single RCT (n=83), reported no significant difference in time taken to control BP to  
216 <150/100mmHg when comparing nifedipine with methyldopa.<sup>34</sup>

### 217 **Vasodilators**

218 Six studies looked at the use of vasodilators (n=252). All utilised hydralazine via a range of  
219 administration routes. Bolus intravenous hydralazine controlled severe hypertension more  
220 quickly than continuous infusion (intervention group 65.23±23.38 minutes, control group  
221 186.36±79.77 minutes: difference -121.13 minutes,  $p<0.001$ ); one quasi-randomised study,  
222 n=15 (postnatal)).<sup>17</sup> Intramuscular hydralazine produced a more significant improvement in  
223 MAP at six hours than intravenous methyldopa (intervention group 104.5mmHg, control  
224 group 112mmHg: difference -7.5mmHg  $p=0.0057$ ) but not at other time points to 24 hours  
225 (one RCT, n=26).<sup>38 39</sup> There was no difference in BP control when comparing oral  
226 hydralazine with oral nifedipine (one RCT, n=38), or intravenous labetalol (one RCT,  
227 n=82).<sup>35 40</sup>

228 Bolus diazoxide was significantly more effective in achieving a target BP of  $\leq 140/90$ mmHg  
229 than intravenous hydralazine (intervention group 67%, control group 43%: RR 0.64, 95% CI  
230 0.46-0.89; one RCT, n=37 (postnatal)).<sup>23</sup> One retrospective cohort study did not present any  
231 statistical analysis.<sup>36</sup>

### 232 **Beta-blockers**

233 Five studies assessed the efficacy of beta-blockers (four RCTs and one retrospective cohort  
234 study, n=305). Two RCTs compared intravenous labetalol with intravenous  
235 hydralazine/dihydralazine: one involved only six postnatal women and presented no  
236 statistical analysis of the data.<sup>24</sup> The other found a significantly greater mean maximal  
237 decrease in MAP with intravenous labetalol (intervention group 25.5±11.2mmHg, control  
238 group 33.3±13.2mmHg: difference -7.8mmHg,  $p=0.02$ ; one RCT, n=32 (postnatal)).<sup>22</sup>  
239 Results conflicted regarding whether oral labetalol was more or less effective than oral

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3 240 nifedipine: a cohort study reported that labetalol controlled BP less rapidly than nifedipine  
4 241 (intervention group 2.7 days, control group 1.7 days: difference 1.0 days,  $p=0.0031$ ; one  
5 242 retrospective cohort study,  $n=128$ ).<sup>41</sup> However, this result was not replicated by an RCT,  
6 243 where the time to BP control was similar in the two groups ( $n=50$ ).<sup>27 28</sup> Neither study  
7 244 demonstrated a difference in the postnatal length of stay ( $n=178$ ). Timolol was effective in  
8 245 decreasing diastolic BP on day one postnatal when compared with methyldopa (intervention  
9 246 group 88.7mmHg, control group 93.8mmHg: difference -5.1mmHg;  $p<0.05$ ; one RCT,  
10 247  $n=80$ ).<sup>42</sup>

### 17 248 *Other antihypertensive medications*

18 249 No statistically significant difference was found between oral clonidine and oral captopril in  
19 250 the incidence of episodes of severe hypertension postpartum (one RCT,  $n=90$ ).<sup>29-31</sup> Two  
20 251 RCTs evaluating indapamide versus methyldopa found no difference in BP control over 6-12  
21 252 months postpartum ( $n=60$ ).<sup>25 37</sup> One retrospective cohort study ( $n=140$ ) compared reserpine  
22 253 with phenobarbital: the results suggested that reserpine might achieve faster and greater BP  
23 254 reduction (data extracted from graphs; no statistical analysis). No adverse events were  
24 255 reported in the intervention group.<sup>43 44</sup>

### 31 256 **What are the benefits and harms of other therapeutic interventions for women with** 32 257 **hypertensive disorders of pregnancy postpartum?**

#### 35 258 *Loop Diuretics*

36 259 Four RCTs ( $n=503$ ) examined loop diuretics versus placebo or usual care in postpartum  
37 260 hypertension management in women with HDP. None reported maternal mortality or safety  
38 261 data. Only two reported major maternal morbidity, neither demonstrating a difference  
39 262 between groups (Table 2b).<sup>16 19</sup>

40 263 One RCT ( $n=120$ ) reported significant improvement in the primary outcome of mean systolic  
41 264 and diastolic BP with oral furosemide versus placebo (magnitude of difference or time points  
42 265 of measurements not stated,  $p<0.001$ ).<sup>45</sup> This was not the case in the other placebo-controlled  
43 266 RCT, which found no significant difference ( $n=19$ ).<sup>46</sup> Two further RCTs ( $n=364$ ) found no  
44 267 significant difference in BP control with oral furosemide versus usual care.<sup>16 19</sup> In one of  
45 268 these, subgroup analysis of women with severe preeclampsia ( $n=70$ ) found women who  
46 269 received oral furosemide had a significantly lower systolic BP day 2 postpartum (intervention  
47 270 group  $142\pm 13$ mmHg, control group  $153\pm 19$ mmHg: difference -11mmHg,  $p<0.004$ ), but not  
48 271 at other time points.<sup>16</sup> In the other trial ( $n=100$ ), furosemide reduced the need for additional

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3 272 antihypertensive treatment during the three days of therapy (intervention group 8.0%, control  
4 273 group 26.0% difference 18%,  $p=0.017$ ), but this difference did not persist to hospital  
5 274 discharge.<sup>19</sup>

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9 275 **Other drugs**

10 276 Five RCTs, one quasi-randomised study and one retrospective cohort study investigated the  
11 277 utility of different drug classes in HDP postpartum (Appendix S5). Three studies reported  
12 278 safety data, but only one reported maternal mortality, demonstrating no difference between  
13 279 groups,<sup>47</sup> and none reported major maternal morbidity (Table 2b).

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18 280 Three small, crossover RCTs examined the use of selective serotonin receptor inhibitors  
19 281 (SSRIs) compared with placebo (n=55). All studies showed a significant reduction in BP with  
20 282 SSRIs compared to placebo (range 25.6 – 34mmHg).<sup>48-50</sup> These data suggest efficacy for this  
21 283 drug class in hypertension management but do not provide any information regarding relative  
22 284 effectiveness compared to standard antihypertensive drugs. Only one study reported safety  
23 285 data: although no statistical analysis was performed, there were a number of side effects  
24 286 reported in the intervention group.<sup>49</sup>

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30 287 Two studies evaluated alternative therapies (n=117): there was no difference in BP control  
31 288 with L-arginine supplementation compared with placebo (one RCT, n=45).<sup>51</sup> One reported  
32 289 accelerated recovery of albuminuria with the administration of shengkangbao (Chinese herbal  
33 290 medicine) versus placebo (one quasi-randomised study, n=72). However, the clinical  
34 291 relevance of this outcome is uncertain, there was no difference between groups in the  
35 292 secondary outcomes of systolic BP, diastolic BP or serum creatinine and no safety data were  
36 293 reported.<sup>52</sup>

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42 294 A single RCT assessed corticosteroids in the management of severe preeclampsia postpartum  
43 295 (n=157).<sup>53 54</sup> No difference was demonstrated between groups in the primary outcome of  
44 296 antihypertensive medication requirement, or in the secondary outcomes of mean arterial  
45 297 pressure (MAP) or need for critical care admission, and no safety data were reported. There  
46 298 were small, statistically significant differences found in some laboratory values (platelet  
47 299 count, lactate dehydrogenase and aspartate transaminase). However, the authors  
48 300 acknowledged that the absolute differences were too small to be clinically relevant.<sup>53</sup>

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55 301 A very small retrospective cohort study suggested an improvement in MAP with the addition  
56 302 of carperitide (atrial natriuretic peptide) to standard therapy (n=16), and no adverse effects

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3 303 related to the intervention were reported.<sup>47</sup> However, the magnitude of the difference was not  
4 304 published, and the study was too small to draw any firm conclusions.

### 305 *Uterine curettage*

306 Six RCTs and two prospective cohort studies (n=837) have explored the role of uterine  
307 curettage in postpartum hypertension management. Uterine curettage is a similar process to  
308 that used in the surgical management of miscarriage: the lining of the uterus is scraped after  
309 completion of the third stage of labour in order to maximise placental tissue removal. This  
310 may be under direct vision following caesarean section, or via the transcervical route  
311 following vaginal birth. The latter approach may be ultrasound-guided and necessitates some  
312 form of anaesthesia. The theory underlying this intervention is that gestational hypertension  
313 and preeclampsia are placenta-mediated, and therefore ensuring complete evacuation of the  
314 uterus following childbirth may accelerate recovery.<sup>55 56</sup>

315 Seven studies explicitly stated they included both participants who delivered vaginally and  
316 those delivered by caesarean: four reported numbers undergoing vaginal delivery (n=248)  
317 and caesarean (n=321). One made no comment about the mode of birth.<sup>57</sup> Only one study  
318 reported maternal mortality: no difference between groups.<sup>15</sup> Two reported major maternal  
319 morbidity, but neither performed any statistical analysis (Table 2b). However, both studies  
320 did suggest a reduction in the absolute number of eclamptic seizures in the curettage group  
321 compared to no intervention.<sup>15 58</sup> In one, however, there was a relevant difference between the  
322 study groups: 28/28 (100%) in the control group were eclamptic at enrolment, compared to  
323 9/20 (45%) in the intervention group.<sup>58</sup> Four studies reported safety data, with none reporting  
324 any complications related to the intervention (Table 2b).<sup>59-62</sup>

325 All eight studies compared curettage with standard care (i.e. no additional intervention), and  
326 all suggested that uterine curettage resulted in a significantly lower BP.<sup>15 18 57-62</sup> One of these  
327 had two control groups: standard care, and oral nifedipine; when compared to oral nifedipine,  
328 no difference was noted with curettage.<sup>60</sup>

329 Five studies reported the magnitude of the difference in MAP between curettage and standard  
330 care: range 6-13mmHg.<sup>15 18 59 60 62</sup> Only two of these reported BP data beyond 24 hours  
331 postpartum: one RCT reported a significantly lower MAP at 48 hours with curettage  
332 (intervention group 104mmHg, control group 113mmHg, difference 9mmHg,  $p=0.0017$ ;  
333  $n=45$ ),<sup>60</sup> but the other RCT demonstrated no significant difference in MAP at 48 hours  
334 ( $n=420$ ).<sup>15</sup>

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3 335 One study demonstrated that a greater proportion of the intervention group attained the target  
4 336 BP of <140/90mmHg at 24 (intervention group 9/20 (45%), control group 3/28 (11%):  
5 337 difference 34%, no *p*-value quoted) and 48 hours postpartum (intervention group 14/20  
6 338 (70%), control group 8/28 (29%): difference 41%, no *p*-value quoted).<sup>58</sup> Two studies did not  
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9 339 present the size of the difference between groups.<sup>57 61</sup>  
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## 11 12 13 **Discussion**

14 341 This review found evidence demonstrating that calcium-channel blockers, vasodilators and  
15 342 beta-blockers lower BP postpartum, but no clear answer to which was most effective and  
16 343 should, therefore, be preferentially prescribed. All but two studies examined the acute control  
17 344 of severe hypertension or short term BP control whilst women remained in hospital  
18 345 postpartum,<sup>25 37</sup> and so provide little guidance about prescription in the weeks after discharge.  
19 346 Moreover these both examined thiazide diuretics, not recommended in the UK for use whilst  
20 347 breastfeeding.<sup>8</sup> Complete safety data were limited across trials, as were data regarding  
21 348 objective clinical outcomes and two further studies examined antihypertensive agents not  
22 349 recommended for use postpartum in the UK (methyldopa and reserpine).<sup>63 64</sup> One trial  
23 350 evaluated captopril at a much higher daily dose than the UK recommended daily starting  
24 351 dose.<sup>64</sup>  
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33 352 Uterine curettage is not currently recommended, due to safety concerns regarding additional  
34 353 anaesthetic and operative risks, and the availability of alternative treatments to lower BP,  
35 354 particularly in the context of vaginal birth.<sup>65</sup> However, the included studies consistently  
36 355 demonstrated that uterine curettage improved BP control versus standard care,<sup>15 18 57-62</sup> with  
37 356 one reporting an equivalent effect to oral nifedipine.<sup>60</sup> Amongst the limited safety data none  
38 357 reported an excess complication rate (infection or uterine damage) with curettage, but given  
39 358 the low incidence of operative complications, the total population (n=837) was likely  
40 359 insufficient to adequately address potential competing risks. Furthermore, these studies did  
41 360 not demonstrate any impact from curettage on maternal mortality or severe morbidity and  
42 361 concerns exist about some studies' methodology. The evidence reviewed is insufficient to  
43 362 recommend incorporation of this intervention into routine clinical practice.  
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53 363 Four trials evaluating loop diuretics failed to provide conclusive evidence of benefit. Three  
54 364 produced non-significant results in their main analysis,<sup>16 19 46</sup> and the single conference  
55 365 abstract which did suggest better BP control with oral furosemide, did not publish the  
56 366 magnitude of the difference, rendering it difficult to assess the clinical relevance.<sup>45</sup> In contrast  
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3 367 to the Cochrane review, we conclude that, at present, there is no evidence to support the  
4 368 routine use of diuretics postpartum.<sup>10</sup>  
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7 369 We found no adequate evidence to support alternative medications or a particular care model  
8 370 in the management of HDP postpartum. SSRIs substantially reduced BP versus placebo,<sup>48-50</sup>  
9 371 but no published data was identified comparing their efficacy with standard antihypertensive  
10 372 treatment, making it difficult to draw meaningful conclusions about their clinical application.  
11 373 Neither study evaluating postpartum care organisation reported maternal mortality or  
12 374 morbidity, or any measure of BP control, with both selecting postnatal readmissions as their  
13 375 primary outcome. An increased postnatal readmission rate, however, may not necessarily  
14 376 reflect harm: it might instead suggest that a particular model of care can better detect  
15 377 problems in the community and admit appropriately, ultimately resulting in a lower risk to  
16 378 patients.  
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24 379 In light of the heterogeneous nature of research in this field, when designing this review, we  
25 380 included all interventions targeting hypertension management, but not end-organ  
26 381 complications, including eclampsia. Therefore, trials evaluating magnesium sulphate were  
27 382 outside the scope of this review. We acknowledge the relevance of this therapy in women  
28 383 with severe pre-eclampsia, especially in the immediate postnatal period, and a Cochrane  
29 384 review suggests there is no uncertainty regarding the effectiveness of this therapy.<sup>66</sup>  
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35 385 A strength of this review is that cohort studies, case-control studies and quasi-randomised  
36 386 studies were eligible in addition to RCTs, and no language or date restrictions were imposed,  
37 387 resulting in a comprehensive review that provides evidence suggesting significant research  
38 388 gaps, consistent with the findings from the Cochrane review (2013).<sup>10</sup> The Cochrane review  
39 389 included only nine trials (author names in bold in Appendix S4). We believe our review adds  
40 390 to this, as an additional 30 studies are included (19 pre-dating the Cochrane search, and 11  
41 391 subsequent to it), providing a current and complete summary of all available research in the  
42 392 field.  
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49 393 The applicability of the findings and recommendations from this review are restricted by the  
50 394 low quality of included studies: both reviewers judged the vast majority to be at high overall  
51 395 risk of bias. Nearly one-quarter of the included studies were published only as conference  
52 396 abstracts, and therefore not subjected to peer review. Data extraction was restricted to the  
53 397 information provided in the abstracts (no authors provided additional data upon request).  
54 398 These were limiting factors in our analysis, but we nonetheless felt it was important to  
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3 399 include these studies for completeness, especially given the paucity of evidence that exists in  
4 400 this field. A further justification for their inclusion is that half of the trials reported in  
5 401 conference abstracts never reach full publication, and positive trials are more likely to be  
6 402 published than negative ones,<sup>67</sup> which has the potential to skew the results of a review if they  
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9 403 are omitted.

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12 404 A further limitation of this review is that the majority of identified studies did not report  
13 405 substantive clinical outcomes such as maternal mortality, morbidity or harms. Without these,  
14 406 it is difficult to define properly the potential role of proposed interventions in clinical  
15 407 practice. The incidence of adverse maternal and neonatal outcomes, particularly in high  
16 408 resource settings, is low meaning adequately powering studies for real outcomes of interest is  
17 409 financially demanding. Therefore researchers often employ surrogate outcomes. Additionally,  
18 410 the range of outcomes reported in included studies was broad and inconsistent, with BP  
19 411 changes in particular being measured in a variety of different ways, further limiting the  
20 412 comparability of trials. Increasingly, core-outcome sets are being produced, with a view to  
21 413 trials reporting as standard, a minimum set of outcomes that are clinically meaningful and  
22 414 important to patients.<sup>68</sup> We hope in future this would enhance our ability to synthesize results  
23 415 from different studies to produce high-quality evidence. There is consensus about trying to  
24 416 move away from surrogate outcomes, for example time to BP control, as they cannot  
25 417 effectively substitute for clinically important outcomes. An important and clinically  
26 418 meaningful end point should measure how a patient feels, functions, or survives.

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29 419 The body of evidence identified was substantially smaller than that underpinning antenatal  
30 420 hypertension management: eighteen studies (n=982), not restricted to RCTs, evaluated  
31 421 antihypertensive medications postpartum. Furthermore, the size of all but a few individual  
32 422 studies was small. In comparison, a Cochrane review (2014) evaluating antihypertensive  
33 423 medication for mild to moderate hypertension in pregnancy included 49 RCTs (n=4,723).<sup>69</sup>  
34 424 Moreover, the quantity and quality of evidence supporting the management of HDP is vastly  
35 425 less than that available for essential hypertension outside pregnancy, where individual RCTs  
36 426 commonly involve several thousand participants.<sup>70</sup>

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39 427 This review demonstrates a lack of good quality evidence for postpartum hypertension  
40 428 management, emphasising the need for further RCTs directly comparing different  
41 429 antihypertensive agents, BP thresholds for medication adjustment and different models of  
42 430 care, with outcome measures other than postnatal readmissions. We believe the studies

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3 431 examining uterine curettage justify further research to evaluate clinically meaningful  
4 432 outcomes and procedural risks. It might be pragmatic to confine this to curettage at caesarean  
5 433 section, given concerns regarding surgical intervention after vaginal birth: an additional  
6 434 anaesthetic is not required; infection risk is lowered within a sterile surgical field compared to  
7 435 the transcervical route, and curettage under direct vision limits perforation risk. This might be  
8 436 beneficial in women with severe preeclampsia where BP control during pregnancy has been  
9 437 challenging despite multiple medications.<sup>55</sup>  
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## **Details of ethical approval**

No ethical approval was required for this project.

## **Contribution to authorship**

AC drafted the protocol with JD and drafted and piloted the data extraction sheet. These were reviewed by RMcM, LP, KT, LM and PL. NR and AC wrote the search strategy, and the online searches were conducted by NR. AC and LP reviewed the search results independently and carried out the data extraction. This manuscript was drafted by AC and reviewed by RMcM, JD, LP, NR, KT, LM and PL. AC will be the guarantor.

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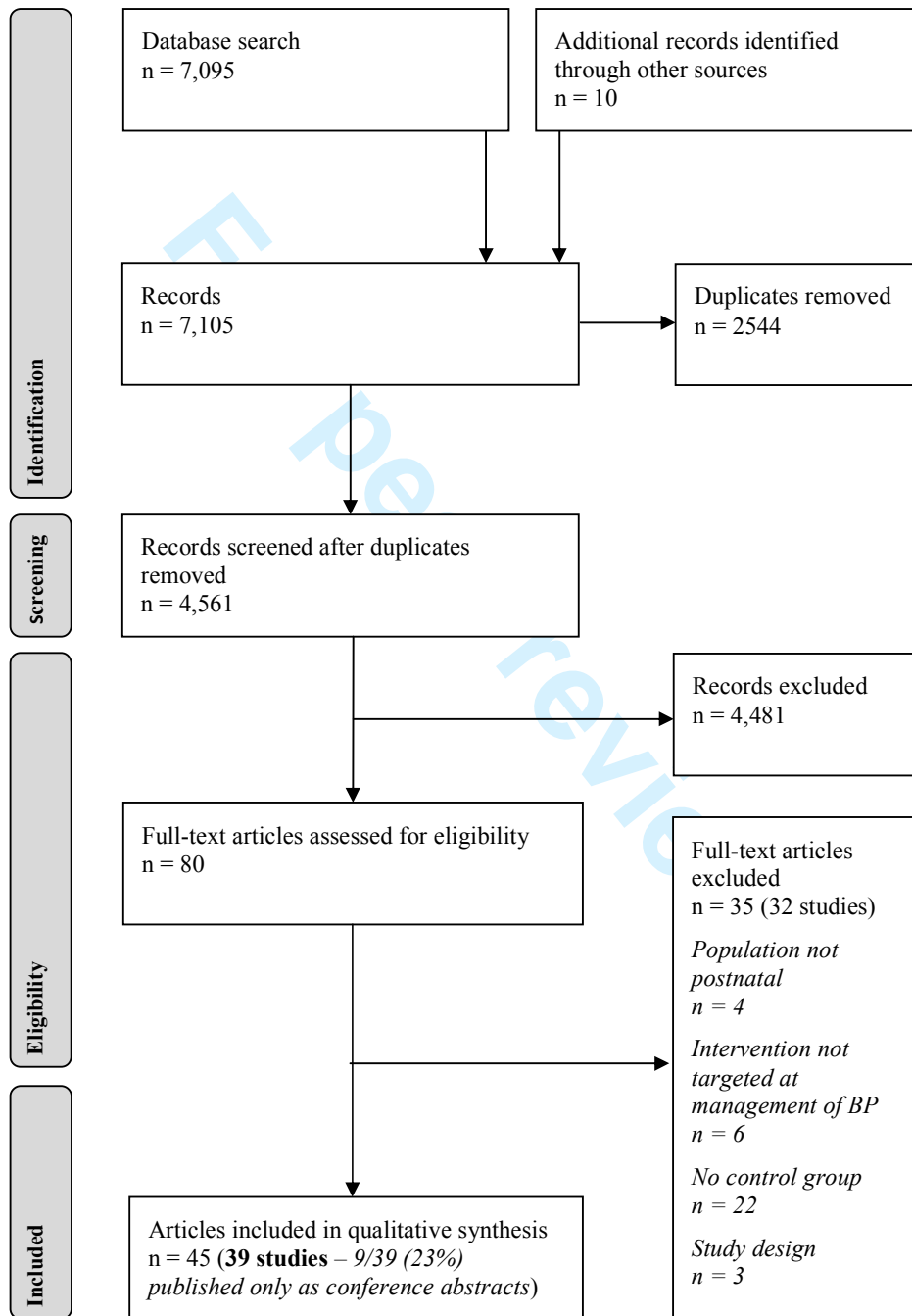


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## Tables and figures

Figure 1: PRISMA Flowchart



**Table 1: Outcome measures**

	<b>Outcome measures</b>	<b>Timing</b>
<b>Primary outcome(s)</b>	Maternal mortality	Direct maternal deaths up to day 42 postpartum; later maternal deaths up to 1 year postpartum
	Maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure; development of preeclampsia with severe features; postnatal complication requiring intervention)	
	Systolic blood pressure control	
	Diastolic blood pressure control	
	Mean arterial pressure control	
	Safety data (adverse events or maternal side effects)	
<b>Secondary outcome(s)</b>	Critical care admission	
	Length of hospital stay following delivery	
	Postnatal readmission to secondary care	
	Antihypertensive medication requirement	
	Urine output	
	Laboratory values Other as defined by study	

Table 2a: Primary outcome and safety data reporting in included studies (Antihypertensive medications, 18 studies)

Study ID	Intervention	Control	Primary outcome assessment			Safety data reporting	Results (for reported outcomes)	
			Maternal mortality	Maternal morbidity	SBP control			DBP control
<b>CALCIUM CHANNEL BLOCKERS (3 studies)</b>								
Barton 1990 <sup>32</sup>	Nifedipine (oral)	Placebo			●	●	●	SBP control: no significant difference. DBP control: no significant difference. MAP control: improved in intervention group (difference 6.3mmHg, p<0.05).
Vermillion 1999 <sup>21</sup>	Nifedipine (oral)	Labetalol (IV bolus)			●	●	●	SBP control: improved in intervention group (difference in time to target BP 18.5 minutes, p=0.002). DBP control: improved in intervention group (difference in time to target BP 18.5 minutes, p=0.002). Safety: no significant difference. 1/25 intervention group became hypotensive.
Sayin 2005 <sup>34</sup>	Nifedipine (oral)	Methyldopa (oral)	●		●	●		Maternal mortality: no significant difference. SBP control: no significant difference. DBP control: no significant difference.
<b>VASODILATORS (6 studies)</b>								
Palot 1979 <sup>36</sup>	Hydralazine (IV infusion) plus furosemide (IV bolus)	Clonidine (IV) plus furosemide (IV bolus)		●				Maternal morbidity: no statistical analysis.
Griffis 1989 <sup>38, 39</sup>	Hydralazine (IM)	Methyldopa (IV bolus)				●	●	MAP control: no significant difference. Safety: no significant difference. No side effects reported in either group.
Walss Rodriguez 1991 <sup>40</sup>	Hydralazine (oral) plus nifedipine (oral, as required)	Nifedipine (oral, as required)			●	●		SBP control: no significant difference. DBP control: no significant difference.
Begum 2002 <sup>17</sup>	Hydralazine (IV bolus)	Hydralazine (IV infusion)				●	●	DBP control: improved in intervention group (difference in time to target DBP 121.1 minutes, p<0.001). Safety: no significant difference. No side effects reported in either group.
Vigil de Gracia 2007 <sup>35</sup>	Hydralazine (IV bolus)	Labetalol (IV bolus)	●	●	●	●	●	Maternal mortality: no significant difference. Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. Small numbers of side effects reported in both groups.
Hennessy 2007 <sup>23</sup>	Diazoxide (IV bolus)	Hydralazine (IV bolus)			●	●		SBP control: improved in intervention group (difference in percentage achieving target BP 23%, p<0.01). DBP control: improved in intervention group (difference in percentage achieving target BP 23%, p<0.01).
<b>BETA BLOCKERS (5 studies)</b>								
Garden 1982 <sup>24</sup>	Labetalol (IV infusion)	Dihydralazine (IV infusion)				●	●	DBP control: no statistical analysis. Safety: no statistical analysis. 1/6 intervention group developed bronchospasm. 4/6 control group developed tachycardia and 1/6 developed oliguria. 4/6 control group – drug stopped due to a precipitous fall of DBP to 40-50mmHg.

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
Fidler 1982 <sup>42</sup>	Timolol (oral)	Methyldopa (oral)			●	●		●	SBP control: improved in intervention group (difference 5.1mmHg, p<0.05). DBP control: no significant difference. Safety: no statistical analysis. 1/40 intervention group became disorientated. 1/40 control group became hypotensive and 1/40 became drowsy.
Mabie 1987 <sup>22</sup>	Labetalol (IV bolus)	Hydralazine (IV bolus)					●	●	MAP control: improved in control group (difference 7.8mmHg (p 0.02)). Safety: no statistical analysis. 1/40 intervention group developed scalp tingling. 2/20 control group developed headaches.
Shumard 2016 <sup>41</sup>	Labetalol (oral)	Nifedipine (oral)			●	●			SBP control: improved in control group (difference in time to achieve target BP 1 day, p=0.0031). DBP control: improved in control group (difference in time to achieve target BP 1 day, p=0.0031).
Sharma 2017 <sup>27 28</sup>	Labetalol (oral)	Nifedipine (oral)			●	●		●	SBP: no significant difference. DBP: no significant difference. Safety: No major side effects reported in either group. Minor side effects more commonly reported in control group (20% intervention, 48% control, p=0.04).
<b>THIAZIDES (2 studies)</b>									
Gaisin 2013 <sup>25</sup>	Indapamide (oral)	Methyldopa (oral)			●	●		●	SBP control: no significant difference. DBP control: no significant difference. Safety: no statistical analysis, no details reported.
Gaisin 2014 <sup>37</sup>	Indapamide (oral) plus ursodeoxycholic acid (oral)	Methyldopa (oral)			●	●		●	SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.
<b>INDOLE ALKALOIDS (1 study)</b>									
Krebs 1956 <sup>43 44</sup>	Reserpine (oral or IM)	Phenobarbital			●	●		●	SBP control: no statistical analysis. DBP control: no statistical analysis. Safety: no statistical analysis. No adverse events reported in intervention group, no comment on control.
<b>CENTRALLY-ACTING ALPHA-AGONISTS (1 study)</b>									
Noronha Neto 2016 <sup>29-31</sup>	Clonidine (oral)	Captopril (oral)	●	●	●	●		●	Maternal mortality: no significant difference. Maternal morbidity: no significant difference. SBP control: improved in intervention group (difference in number of episodes of high BP (1.4, p<0.08)). DBP: improved in intervention group (difference in number of episodes of high BP (1.4, p<0.08)). Safety: no significant difference. Adverse reactions 18.6% intervention, 28.8% control, p=NS.

**Table 2b: Primary outcome and safety data reporting in included studies (Loop diuretics, other drugs, uterine curettage and organisation of care, 21 studies)**

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
<b>LOOP DIURETICS (4 studies)</b>									
Matthews 1997 <sup>46</sup>	Furosemide (oral)	Placebo					●	MAP control: no significant difference.	
Ascarelli 2005 <sup>16</sup>	Furosemide (oral)	No intervention		●	●	●		Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference.	
Amorim 2015 <sup>45</sup>	Furosemide (oral)	Placebo			●	●	●	SBP control: improved in intervention group (difference not stated, p<0.001). DBP control: improved in intervention group (difference not stated, p<0.001). MAP control: improved in intervention group (difference not stated, p<0.001).	
Veena 2017 <sup>19</sup>	Furosemide (oral) + nifedipine (oral)	Nifedipine (oral)		●	●	●	●	Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference.	
<b>OTHER DRUGS (7 studies)</b>									
<b>Selective 5-HT antagonists</b>									
Weiner 1982 <sup>48</sup>	R41468 (intravenous infusion)	Placebo					●	MAP control: improved in intervention group (difference 25.6mmHg, p<0.001). SBP control: improved in intervention group (difference in SBP decline 34mmHg, p<0.001). DBP control: improved in intervention group (difference in DBP decline 27mmHg, p<0.001).	
Weiner 1984 <sup>49</sup>	Ketanserin (IV infusion)	Placebo		●	●	●	●	MAP control: improved in intervention group (difference not stated, p<0.001) Safety: No statistical analysis. 3/20 intervention group experienced blurred vision: 1 of these was hypotensive (responded to hydration). 1/20 intervention group experienced mild euphoria.	
Montenegro 1985 <sup>50</sup>	Ketanserin (IV bolus +/- infusion)	Placebo		●	●	●	●	SBP control: improved in intervention group (absolute difference not stated, p<0.001). DBP control: improved in intervention group (absolute difference not stated, p<0.001). MAP control: improved in intervention group (absolute difference not stated, p<0.001).	
<b>Alternative therapies</b>									
Hladunewich 2006 <sup>51</sup>	L-arginine (oral or IV bolus)	Placebo			●	●	●	SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.	
Liu 2009 <sup>52</sup>	Shengkangbao (oral or IV bolus)	No intervention			●	●		SBP control: no significant difference. DBP control: no significant difference.	

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
<b>Steroids</b>									
Barrilleaux 2005 <sup>53 54</sup>	Dexamethasone (IV bolus)	Placebo					●	MAP control: no significant difference.	
<b>Atrial natriuretic peptide</b>									
Shigemitsu 2015 <sup>47</sup>	Carperitide (route not specified)	No intervention	●				●	Maternal mortality: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.	
<b>UTERINE CURETTAGE (8 studies)</b>									
Salvatore 1967 <sup>58</sup>	Uterine curettage	No intervention		●	●	●		Maternal morbidity: no statistical analysis. SBP control: no statistical analysis. DBP control: no statistical analysis.	
Magann 1993 <sup>59</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at different time points to 24h postpartum 6-10mmHg, p<0.05). Safety: no significant difference. No complications reported from intervention (follow-up to 7 weeks postpartum).	
Magann 1994 <sup>60</sup>	Uterine curettage	Nifedipine (oral) or no intervention					●	MAP control: no significant difference between intervention and oral nifedipine; improved in intervention group compared to no intervention (difference at 8-48h postpartum 9-13mmHg, p=0.0017). Safety: no significant difference. No complications/side effects reported from interventions (follow-up to 7 weeks postpartum).	
Gocmen 1996 <sup>57</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, p=0.01).	
Gomez 2005 <sup>61</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, p<0.001). Safety: no significant difference. No complications reported from intervention.	
Alkan 2006 <sup>62</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference 6.8mmHg, p<0.05). Safety: No significant difference. No complications reported from intervention.	
Ragab 2013 <sup>15</sup>	Uterine curettage	No intervention	●	●			●	Maternal mortality: no significant difference. Maternal morbidity: no statistical analysis. MAP control: improved in intervention group (difference at 6h postpartum 12.3mmHg, P=0.02, difference at 24h postpartum 9.2mmHg, p=0.01)	
Mallapur 2015 <sup>18</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at 4h postpartum 7.6mmHg, p<0.001).	
<b>ORGANISATION OF CARE (2 studies)</b>									
York 1997 <sup>26</sup>	Nurse specialist follow-up	No intervention						N/A	
Bibbo 2014 <sup>33</sup>	Specialist postpartum clinic	No intervention						N/A	



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**Legend for Tables 2a&b**

● = improved in intervention group; ● = no significant difference; ● = improved in control group; ● = unclear

For primary outcome assessment where there was a significant difference between groups, the magnitude of the difference is reported; where any adverse events or side effects were reported this is presented

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**Appendix S1: Management of hypertensive disorders of pregnancy in the postpartum period: A systematic review protocol**

**Registration:** PROSPERO CRD42015015527

[http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015015527#.VL4ZI9KsWcK](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527#.VL4ZI9KsWcK)

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**Amendments:** Protocol first published 22/12/2014 (version 1.0). Protocol amended (version 2.0 25/03/2015) to include all reporting items from the PRISMA-P 2015 checklist, and PROSPERO registration number.

**Review funder:** NIHR Collaborations for Leadership in Applied Health Research and Care (funding A Cairns' fellowship)

**Review sponsor:** University of Oxford

**Abstract**

**Rationale:** Hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia) are a leading cause of direct maternal death in the UK, and affect approximately 5-10% of pregnancies. Hypertensive disorders of pregnancy persist during the postpartum period, and complications can occur during this time.

**Research question:** How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

**Objectives:**

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

**Search strategy:** Medline and nine other electronic databases will be searched for articles published from inception until October 2014 using a search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period.

**Study eligibility criteria:**

*Population:* postnatal women with gestational hypertension or pre-eclampsia as defined by study

*Intervention:* therapeutic intervention for hypertensive disorders of pregnancy

*Comparisons:* another intervention, placebo or no intervention

*Study design:* RCT, prospective or retrospective cohort study or case-control study

*Publication date:* no restrictions

*Language:* no restrictions

**Data management and extraction:** Two reviewers will first review the titles of articles yielded by the search, and then the abstracts of articles of potential relevance. The full papers of potentially eligible papers will be assessed, and data extracted independently by the two reviewers using a data extraction sheet. Differences in study selection and data extraction will be resolved by discussion.

**Assessment of methodological quality:** This will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, and for the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales.

**Systematic review registration:** This systematic review is registered with PROSPERO (International prospective register of systematic reviews).



## Rationale

### *Definitions*

The National Institute for Health and Clinical Excellence (NICE) defines gestational hypertension as new-onset raised blood pressure ( $\geq 140/90$ mmHg) beyond 20 weeks gestation. NICE defines pre-eclampsia as new-onset raised blood pressure ( $\geq 140/90$ mmHg) together with new-onset significant proteinuria ( $\geq 300$ mg/24hr), beyond 20 weeks gestation (1).

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as new-onset raised blood pressure (as defined by NICE) in association with one of new-onset significant proteinuria (as defined by NICE), maternal organ dysfunction or uteroplacental insufficiency (2).

### *Epidemiology*

Hypertensive disorders of pregnancy remain the second commonest direct cause of maternal death in the USA (3). Until recently this has also been the case in the UK (CMACE 2006-8)(4), but the most recent Confidential Enquiry into maternal deaths showed that for the triennium 2009-11, pre-eclampsia and eclampsia was the fourth commonest cause of direct death (behind thrombosis, genital tract sepsis and haemorrhage), with a rate of 0.42 deaths per 100,000 maternities (5).

A recent population-based retrospective study in the United States found the rate of pre-eclampsia to be 3.4%. This study showed a slight, but significant increase, in the rates of both mild, and to a greater extent, severe pre-eclampsia over the period studied (1980-2010) (6).

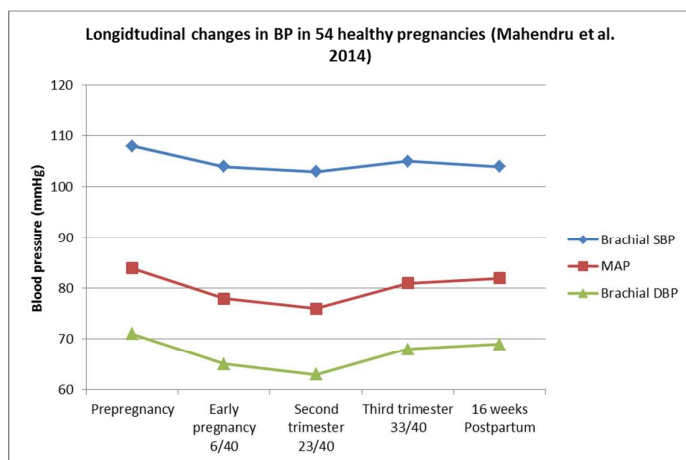
Reviews of the literature, and national guidelines, quote rates of gestational hypertension between 6% (7) and 15% (8). A retrospective study using data from the National Hospital Discharge Survey in the United States (1987-2004) demonstrated an incidence of 30.6 cases of gestational hypertension per 1000 deliveries in 2003-2004 (3.1%) (9). In a well-designed large randomised controlled trial assessing preventative strategies for hypertensive disorders of pregnancy in low risk, nulliparous women the incidence of gestational hypertension across both groups was 6% (10).

### *Physiology of blood pressure in pregnancy and postpartum*

As a result of a significant decrease in systemic vascular resistance (as early as 5 weeks gestation) (11) there is a decrease in arterial pressures from early in the first trimester. Arterial pressures reach a nadir in the second trimester, and then begin to rise in the third trimester, before reaching near-preconception levels in the postnatal period (12).



Figure 1: Serial blood pressures before, during and after pregnancy (reproduced from the data of Mahendru et al. 2014) (12)



In gestational hypertension and pre-eclampsia the normal pregnancy-induced vasodilatation is reversed. In untreated women with pre-eclampsia significant increases in systemic vascular resistance are seen and result in elevation of blood pressure (13).

#### ***Hypertensive disorders of pregnancy in the postpartum period***

There has been considerable focus on blood pressure control during pregnancy, especially with respect to pregnancy outcome. However, it is recognised that hypertensive disorders of pregnancy do persist during the postpartum period, and that complications can occur during this time. A small retrospective observational study published in 1987 looked at 67 women with moderate-severe pre-eclampsia: there was often an initial decrease in blood pressure after delivery, but this was followed by a rise to hypertensive levels in many women. In 50% of cases the blood pressure was 150/100mmHg or higher on day 5 after birth. The authors recommended continuing blood pressure monitoring and treatment in the postpartum period for women with a diagnosis of pre-eclampsia (14).

Most women with hypertensive disorders of pregnancy will be treatment-free by 3 months postpartum. In women whose blood pressure normalised after delivery the mean time to normalisation in a retrospective cohort study of 62 women was 5.4 weeks (15). This rapidly changing blood pressure, with shifting medication requirement, poses an additional challenge in terms of how best to manage this down-titration.

Approximately one third of eclamptic seizures occur postpartum, and studies suggest that over half of these seizures occur more than 48 hours after birth. Chames et al. (2002) highlight the importance of education of women and clinicians regarding prodromal symptoms of eclampsia in the postnatal



period (16). A case series published in 2005 of patients who sustained a stroke in association with severe pre-eclampsia or eclampsia, showed that more than half (57%) of these strokes occurred in the postpartum period (17).

### ***Current guidelines***

NICE guidelines highlight that very few clinical studies have addressed the management of blood pressure postpartum, and in practice clinical care is typically to continue antepartum antihypertensive medication and monitor blood pressure in the community with a focus on prevention of over-treatment.

NICE recommend frequency of monitoring in the postnatal period for both pre-eclampsia and gestational hypertension. The guidelines also stipulate thresholds for considering increasing or starting anti-hypertensive medication during this period (150/100 mmHg), and for reduction or stopping anti-hypertensive medication (consider at < 140/90 mmHg, and reduce at < 130/80 mmHg) (1).

### **Research question**

How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

### **Objectives**

The aim is to establish what evidence exists to guide the optimal approach to management of gestational hypertension and pre-eclampsia in the postnatal period. We want to address the specific sub-questions:

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

### **Information sources and search strategy**

The systematic review of 'management of hypertensive disorders of pregnancy in the postpartum period' will be conducted in line with the PRISMA statement (18). Completion of a systematic review



is an iterative process, and it may be that modifications to the original review protocol are required during its conduct.

A search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period will be developed by an experienced trial search co-ordinator. Potentially relevant studies will be identified following screening of title and abstract of studies captured by the search and full text assessed for suitability.

Resources to be searched from inception to October 2014:

- Medline (Appendix 3) and 9 other electronic databases
- Trial registers (ClinicalTrials.gov; Current Controlled Trials; WHO; PROSPERO)
- Meta Search Engines
- Hand searches of reference lists
- Citation searching on Scopus and Web of Science
- Related articles search on PubMed
- Contact with authors and professional bodies / organisations: Experts in this field will be contacted for their recommendations of potentially relevant citations (19)

## Study eligibility criteria

### **INCLUSION CRITERIA**

**Population:** postnatal women with hypertensive disorders of pregnancy (gestational hypertension or pre-eclampsia).

**Intervention:** therapeutic intervention for management of hypertensive disorders of pregnancy

**Comparisons:** other intervention, placebo or no intervention

**Study design:** randomised controlled trial, cohort study (prospective and retrospective) or case-control study; human studies only

**Publication Date:** no restrictions

**Language:** no restrictions

### **EXCLUSION CRITERIA**

Exclude report / study if **any** exclusion criteria fulfilled:

**Population:** antenatal or intrapartum women with hypertensive disorders of pregnancy; end-organ complications of pre-eclampsia (eclampsia, renal failure, HELLP syndrome)



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**Intervention:** treatment of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets); prevention or management of eclampsia; prevention of postpartum hypertension; choice of anaesthetic or sedative in pre-eclampsia; observational studies

**Comparisons:** no control group

**Study design:** guidelines, reviews, expert opinions, letters, commentaries, audits, case series and case reports excluded; animal studies

### Data extraction

Two reviewers (AC and LP) will screen the titles and abstracts of articles yielded by the search against the eligibility criteria. Discrepancies will be resolved by consensus before determining the list of full papers for review. The reports will be screened independently by the two reviewers, and discrepancies will be resolved by discussion before deciding which papers to include in the review.

Data from included studies will be extracted independently by the two reviewers using a piloted and standardised data extraction sheet. Differences in data extraction will be resolved by discussion.

In the event that there is more than one report published about a single study: the reports will be reviewed separately but the data from that study grouped in our analysis, and the primary reference will be used.

In the event that data is missing from a report (for example the sole publication is a conference abstract) we will contact the authors directly to request further detail.

The study characteristics (study size, population, setting, study design, methodology, intervention, controls if applicable, outcome measures, and follow up period) will be recorded and reported.

### Data synthesis

The data extracted will be aggregate.

Due to the heterogeneous nature of the outcomes reported in these studies a narrative synthesis is planned.

For trials where the population study is peripartum (i.e. a mixture of antepartum, intrapartum and postpartum) we will extract the data for the postpartum women and analyse this. If this is not feasible from the reported data then we will contact the study authors to request the data for this subgroup.

### Outcomes

The results of all clinically relevant outcomes in hypertensive disorders of pregnancy that would be important to clinicians and patients will be extracted and reported.

The main outcomes we are interested in are listed in table 1 below:





Table 1

	Outcome measures	Timing
<b>Primary outcome(s)</b>	Maternal mortality Major maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure) Systolic blood pressure control Diastolic blood pressure control Mean arterial pressure control	Direct maternal deaths upto day 42 postpartum; later maternal deaths upto 1 year postpartum
<b>Secondary outcome(s)</b>	Critical care admission Postnatal readmission to secondary care Length of hospital stay following delivery Anti-hypertensive medication requirement Maternal side effects of intervention Development of pre-eclampsia with severe features Postnatal complication requiring intervention Urine output Laboratory values	

### Assessment of methodological quality

We will assess the risk of bias in each study. For randomised trials this will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Appendix 1, Table 2) (20). For each study the key domains will be identified, and then an overall assessment of bias within each trial made, according to the guidance published by the Cochrane Collaboration (Appendix 1, Table 2).

For the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales (Appendix 2, Tables 4 and 5) (21).

We will make a global assessment of bias across trials, based on the guidance from the Cochrane Collaboration (Appendix 1, Table 3):

- EITHER Most information is from trials at low risk of bias;
- OR most information is from trials at low or unclear risk of bias;
- OR the proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

**Discussion**

A Cochrane Review (2013) addresses the question of 'prevention and treatment of postpartum hypertension'. This only includes randomised controlled trials (9 in total), and does not address the issue of monitoring blood pressure during this period (22). Given the paucity of evidence cited in this area we believe there is a place for a review looking at all available evidence for the optimal approach to management of hypertensive disorders of pregnancy in the postpartum period.

**Conflicts of interest**

Neither AC nor LP have any conflicts of interest.

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## Appendix 1

**Table 2:** Cochrane Collaboration's tool for assessing risk of bias (*adapted from Higgins and Altman*)(20)

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what	Reporting bias due to selective



		was found	outcome reporting
	Anything else, ideally	State any important concerns	Bias due to
<b>Other bias</b>	Pre-specified	about bias not covered in the other domains in the tool	problems not covered elsewhere

\*Assessments should be made for each main outcome or class of outcomes.

**Table 3:** Approach to formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials (*adapted from Higgins and Altman*)(20)

Risk of bias	Interpretation	Within a trial	Across trials
<b>Low risk of bias</b>	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
<b>Unclear risk of bias</b>	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
<b>High risk of bias</b>	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results



## Appendix 2

**Table 4: Newcastle-Ottawa quality assessment scale case control studies(21)**

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

<b>Selection</b>	Is the case definition adequate?	a) Yes, with independent validation * b) Yes, e.g. record linkage or based on self-reports c) No description
	Representativeness of the cases	a) Consecutive or obviously representative series of cases * b) Potential for selection biases not stated
	Selection of controls	a) Community controls * b) Hospital controls c) No description
	Definition of controls	a) No history of disease (endpoint) * b) No description of source
<b>Comparability</b>	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the most important factor) * b) Study controls for any additional factor *
<b>Exposure</b>	Ascertainment of exposure	a) Secure records (e.g. surgical records) * b) Structured interview where blind to case/control status * c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description
	Same method of ascertainment for cases and controls	a) Yes * b) No
	Non-response rate	a) Same rate for both groups * b) Non-respondents described c) Rate different and no designation

**Table 5: Newcastle-Ottawa quality assessment scale cohort studies(21)**

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

<b>Selection</b>	Representativeness of the exposed cohort	a) Truly representative of the average <<_>> (describe) in the community * b) Somewhat representative of the average <<_>> (describe) in the community ☐ c) Selected group of users e.g. nurses, volunteers d) No description of the derivation of the cohort
	Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort * b) Drawn from a different source c) No description of the derivation of the non-exposed cohort
	Ascertainment of exposure	a) Secure record (e.g. surgical records) * b) Structured interview * c) Written self-report d) No description



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	Demonstration that the outcome of interest was not present at start of study	a) Yes * b) No
<b>Comparability</b>	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the post important factor) * b) Study controls for any additional factor *
<b>Outcome</b>	Assessment of outcome	a) Independent blind assessment * b) Record linkage * c) Self-report d) No description
	Was follow-up long enough for outcomes to occur	a) Yes (select an adequate follow up period for outcome of interest) * b) No
	Adequacy of follow-up of cohorts	a) Complete follow-up – all subjects accounted for * b) Subjects lost to follow-up unlikely to introduce bias: >_ % (select an adequate %) follow-up rate, or description provided of those lost) * c) Follow-up rate < _ % (select an adequate %) and no description of those lost d) No statement





### Appendix 3: Medline search strategy

# ▼	Searches	Results
1	Pregnancy/ and Hypertension/	9226
2	exp Hypertension, Pregnancy-Induced/	29022
3	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or antenatal or antepart* or ante-part* or obstetric*) and (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti.	6787
4	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or antenatal or antepart* or ante-part* or obstetric*) adj3 (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti,ab.	12434
5	(eclamp* or preeclamp* or pre-eclamp* or hellp).ti,ab.	25194
6	1 or 2 or 3 or 4 or 5	46611
7	Postnatal Care/	4044
8	Aftercare/	6684
9	Postpartum Period/ and Maternal Health Services/	126
10	exp Puerperal Disorders/ and Maternal Health Services/	196
11	Postpartum period/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	187
12	exp Puerperal disorders/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	237
13	Postpartum period/ and exp Curettage/	30
14	exp Puerperal disorders/ and exp Curettage/	118
15	Postpartum period/ and hypertension/dt, th	33
16	exp Puerperal disorders/ and hypertension/dt, th	54
17	exp Puerperal disorders/dt, th	6408
18	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (care or healthcare or service* or program* or scheme* or intervention*)).ti,ab.	4407
19	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (clinic? or unit? or visit* or referral? or appointment?)).ti,ab.	1491
20	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (manage* or treat* or therap* or medication? or recovery)).ti,ab.	7287
21	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (antihypertens* or anti-hypertens* or calcium channel block* or beta block* or b block* or ace inhibitor* or angiotensin converting enzyme inhibitor* or diuretic*)).ti,ab.	41
22	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (evaluat* or assess* or screen* or diagnos* or monitor* or follow up or supervis*)).ti,ab.	7562
23	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 curet*).ti,ab.	82
24	(postnatal or post-natal or postpart* or post-part* or puerper*).ti.	41491
25	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	64775



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26	6 and 25	1896
27	((postnatal or post-natal or postpart* or post-part* or puerper*) and (hypertens* or blood pressure)).ti.	270
28	26 or 27	1990
29	exp animals/ not humans.sh.	4079856
30	(rat or rats or rodent? or mice or mouse or cow or cows or cattle or calf or calves or ewe? or sheep or goat or ruminant? or pig or pigs or minipig? or chicken? or horse or horses or murine or bovine or ovine or porcine or animal?).ti.	1682619
31	29 or 30	4373527
32	28 not 31	1881

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## Appendix S2: PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7; Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7 (narrative)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	N/A



## Appendix S2: PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7; Appendix S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8; Appendix S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13; Tables 2a+b; Appendix S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8; Appendix S6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17



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*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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**Appendix S3: Primary reasons for article exclusion (n = 35)**

	Population not postnatal	Intervention not targeted at management of BP	No control group	Study design
<b>n</b>	4	6	22	3
<b>Study IDs</b>	Berks 2015 Gerard 1983 Scardo 1999 Wacker 2006	Chandrasekaran 2015 Ehrenberg 2004 Ehrenberg 2006 Ossada 2016 Wasden 2012 Younger-Lewis 2016	Al Waili 2004 Alicino 1962 Barton 1991 Belfort 1988 Belfort 1992 Bittle 2014 Bosio 2003 Correa 1982 Dulitzky 1987 Hirshberg 2016 Hirshberg 2017 Hunter 1961 Onishi 2015 Robinson 1964 Rodriguez 2012 Saghir Smith 2005 Sukerman-Voldman 1985 Taslimi 1991 Tkacheva 2006 Wacker 1994 Walters 1984	Editor, Emergency Medicine 1990 Cursino 2015 Gallegos 1961

## APPENDIX S4: Main characteristics of included studies (n=39)

Study ID	Methods		Participants			Intervention		Outcomes		
	Study design	Duration	n*	Age (yr) <sup>†</sup>	Setting	Country	Intervention	Control(s)	Primary	Secondary
<b>ANTIHYPERTENSIVE MEDICATIONS (18 studies)</b>										
<b>Calcium channel blockers</b>										
Barton 1990 <sup>32</sup>	RCT	Enrolled immediately after birth Follow-up (F/U) 48h	31	24.0 26.3	Tertiary referral hospital	USA	Nifedipine 10mg oral (PO) 4-hourly for 48 hours	Placebo	Mean arterial pressure (MAP)	Systolic blood pressure (SBP ) Diastolic blood pressure (DBP) Maternal heart rate Antihypertensive medication requirement Urine output Laboratory values (urine protein, creatinine clearance, haematocrit (HCT), platelets (plt), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, serum electrolytes, uric acid (UA), urine specific gravity)
Vermillion 1999 <sup>21</sup>	RCT	Enrolled within 24h of birth F/U 3 – 24h	21	27.2±7.3 27.0±6.4	Tertiary referral hospital	USA	Nifedipine 10mg stat PO then 20mg every 20 minutes until BP <160/110 or max 5 doses + intravenous (IV) placebo	Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or max 5 doses (300mg) + oral placebo	SBP + DBP	SBP (failure to achieve target <160mmHg) DBP (failure to achieve target <110mmHg) Maternal side effects Antihypertensive medication requirement Urine output
Sayin 2005 <sup>34</sup>	RCT	Enrolled 24h after birth F/U 72h after BP controlled	83	17-41	Tertiary referral hospital	Turkey <sup>‡</sup>	Nifedipine 10mg PO QDS until BP <150/100mmHg for 48h	Methyldopa 250mg PO TDS	SBP + DBP	Maternal mortality Antihypertensive medication requirement Hypertensive retinopathy
<b>Vasodilators</b>										
Palot 1979 <sup>36</sup>	Retrospective cohort study	Not specified	54	24.5 (17-37)	Not specified	France <sup>†</sup>	Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose	(1) Clonidine IV and furosemide 20mg IV stat OR (2) Non-systematic treatment	Maternal morbidity (development of pre-eclampsia with severe features)	BP (time to resolution of hypertension)
Griffis 1989 <sup>38</sup> 39	RCT	F/U 24h	26	Not specified	Tertiary referral hospital	USA	Hydralazine 20mg IM QDS for 24h	Methyldopa 250mg IV QDS x 24h	MAP	Maternal side effects Antihypertensive medication requirement Urine output (time to diuresis)
Walls Rodriguez 1991 <sup>40</sup>	RCT	Not specified	38	16-40	Not specified	Mexico <sup>†</sup>	Hydralazine 40mg PO QDS, duration not specified + if DBP > 110 PRN nifedipine 10mg SL every 30 minutes, to maximum of 3 doses	Nifedipine 10mg sub-lingual (SL) every 30 minutes if DBP ≥110mmHg	SBP	DBP Antihypertensive medication requirement
Begum 2002 <sup>17</sup>	Quasi-randomised trial	Not specified	15	24.09±4.93 22.72±5.08	Tertiary referral hospital	Bangladesh	Hydralazine 5mg then 2mg IV bolus every 15 minutes until DBP 90-95mmHg	Hydralazine 20mg/200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15 min intervals; until DBP 90-95mmHg	DBP	Maternal side effects Antihypertensive medication requirement Maternal heart rate
Vigil-De Gracia 2007 <sup>35</sup>	RCT	Enrolled day 2-3 after birth F/U not specified	82	29.9±5.9 31.3±5.5	Tertiary referral hospital	Panama	Hydralazine 5mg IV every 20 minutes until BP <160/110 or max 5 doses	Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or max 5 doses (300mg)	SBP + DBP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) Maternal side effects Antihypertensive medication requirement Maternal heart rate
Hennessy 2007 <sup>23</sup>	RCT	F/U 3h	37	21-43 (mean 33)	Tertiary referral hospital	Australia	Diazoxide 15mg IV every 3 minutes, maximum dose 300mg	Hydralazine 5mg IV every 20 minutes, maximum 15mg	SBP + DBP	SBP (10mmHg above target after 1 hour) DBP (10mmHg above target after 1 hour) Maternal side effects (including hypotension) Time taken to administer drug
<b>Beta blockers</b>										
Fidler 1982 <sup>42</sup>	RCT	Enrolled 4 days after birth F/U 9 days	80	29.7±1.0 27.8±0.9	Tertiary referral hospital	UK	Timolol 5mg PO TDS for 9 days	Methyldopa 250mg PO TDS for 9 days	DBP	SBP DBP (time to achieve control, proportion achieving control) Maternal side effects
Garden 1982 <sup>24</sup>	RCT	Enrolled immediately after birth F/U 45-64h	6	25-44 20-28	Tertiary referral hospital	South Africa	Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 160mg/h	Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 80mg/h	DBP	Maternal side effects
Mabie 1987 <sup>22</sup>	RCT	Enrolled 1-96 hours after birth F/U 3h	41	23.7±6.9 22.9±7.0	Tertiary referral hospital	USA	Labetalol 20mg IV every 10 minutes then escalating until DBP <100mmHg or maximum cumulative dose reached (300mg)	Hydralazine 5mg IV every 10 minutes until DBP <100mmHg	MAP	MAP (time to maximal decrease) DBP (achieving target <100mmHg) Maternal side effects Antihypertensive medication requirement Maternal heart rate

\* n = postnatal population (antenatal excluded)

† If given separately, intervention group followed by control group

‡ Non-English language manuscript

Study ID	Methods		Participants				Intervention		Outcomes	
	Study design	Duration	n*	Age (yr) <sup>†</sup>	Setting	Country	Intervention	Control(s)	Primary	Secondary
Shumard 2016 <sup>41</sup>	Retrospective cohort study	F/U not specified (but >24h)	128	Not specified	Not specified	USA	Labetalol PO (variable dose and frequency)	Nifedipine PO (variable dose and frequency)	Length of hospital stay after birth	SBP DBP Antihypertensive medication requirement
Sharma 2017 <sup>27, 28</sup>	RCT	4-6 weeks (BP outcomes) 6 months (duration antihypertensive medication)	50	34.0±7.4 33.3±6.4	Tertiary referral hospital	USA	Labetalol 200mg PO BD	Nifedipine XL 30mg PO OD	SBP + DBP	Maternal side-effects Length of hospital stay after birth Antihypertensive medication requirement
<b>Thiazides</b>										
Gaisin 2013 <sup>25</sup>	RCT	6 months	30	23-29	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD, duration unclear	Adjusted dose methyldopa	SBP + DBP	Safety data Laboratory values (lipid and glucose metabolism) Adherence to treatment Weight reduction Decrease in albuminuria Decrease in LV mass index Endothelial function Milk production
Gaisin 2014 <sup>37</sup>	RCT	1 year	30	24-28	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD with ursodeoxycholic acid 250mg PO TDS, duration unclear	Adjusted dose methyldopa	SBP + DBP	Maternal side effects Laboratory values (atherogenic lipid profile, glucose metabolism, renal function) Offspring adverse events Weight reduction Decrease in microalbuminuria Decrease in LV mass index Endothelial function
<b>Indole alkaloids</b>										
Krebs A 1956 <sup>43, 44</sup>	Retrospective cohort study	F/U not specified (but >24h)	140	Not specified	Not specified	Switzerland <sup>†</sup>	Reserpine 0.25mg PO or IM TDS or QDS for 7 days	Phenobarbital	SBP + DBP	SBP + DBP (non-responders) Maternal side effects Resolution of albuminuria Resolution of oedema
<b>Centrally-acting alpha-agonists</b>										
Noronha Neto 2016 <sup>29-31</sup>	RCT	Enrolled immediately after birth F/U 4 days	90	28.9±6.7 28.8±6.7	Tertiary referral hospital	Brazil	Clonidine 0.1mg PO repeated every 20 minutes to maximum 6 doses	Captopril 25mg PO repeated every 20 minutes to maximum 6 doses	SBP + DBP	SBP (% reduction) SBP + DBP (daily mean) Maternal side effects Antihypertensive medication requirement
<b>LOOP DIURETICS (4 studies)</b>										
Matthews 1997 <sup>46</sup>	RCT	Enrolled 12-24h after birth F/U 6 weeks	19	Not specified	Tertiary referral hospital	UK	Furosemide 40mg PO OD for 7 days	Placebo	MAP	Length of hospital stay after birth Antihypertensive medication requirement Urine output Laboratory values (hypokalemia)
Ascarelli 2005 <sup>16</sup>	RCT	Enrolled 2-24h after birth F/U 6 weeks	264	22.8±6.1 22.9±6.0	Tertiary referral hospital	USA	Furosemide 20mg PO OD + potassium 20mEq PO OD for 5 days	No intervention	SBP	Maternal morbidity (postnatal complication requiring intervention) DBP Length of hospital stay after birth Antihypertensive medication requirement Maternal weight Maternal HR Duration of magnesium sulphate
Amorim 2015 <sup>45</sup>	RCT	Enrolled immediately after birth F/U 5 days	120	Not specified	Tertiary referral hospital	Brazil	Furosemide 40mg PO OD, duration not specified	Placebo	SBP + DBP	MAP SBP (daily episodes ≥180mmHg) DBP (daily episodes ≥110mmHg) Length of hospital stay after birth Antihypertensive medication requirement Urine output Maternal heart rate
Veena 2017 <sup>19</sup>	RCT	Enrolled <24h after birth F/U until hospital discharge	100	24.34±4.31 24.02±4.27	Tertiary referral hospital	India	Furosemide 20mg PO OD + nifedipine 10mg PO TDS for 3 days	Nifedipine 10mg PO TDS for 3 days	SBP + DBP	MAP Maternal morbidity (postnatal complication requiring intervention) Length of hospital stay after birth Antihypertensive medication requirement Urine output
<b>OTHER DRUGS (7 studies)</b>										
<b>Selective 5-HT antagonists</b>										
Weiner 1982 <sup>48</sup>	RCT (crossover)	F/U not specified	5	Not specified	Tertiary referral	USA	R41468 IV (dose not specified) bolus then infusion for 90 minutes	Placebo	MAP	MAP (rate at which hypertension returned post infusion) Urine output (infusion related diuresis)



Study ID	Methods		Participants			Intervention		Outcomes		
	Study design	Duration	n*	Age (yr) <sup>†</sup>	Setting	Country	Intervention	Control(s)	Primary	Secondary
Weiner 1984 <sup>49</sup>	RCT (crossover)	Enrolled immediately after birth F/U 3.5h	20	28±6.4	Tertiary referral	USA	Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5 minutes if no response.	Placebo	SBP + DBP	Maternal side effects DBP (achieving target <95mmHg) MAP Antihypertensive medication requirement Response rate
Montenegro 1985 <sup>50</sup>	RCT (crossover)	Enrolled immediately after birth F/U not specified	30	21.5 (13-31)	Tertiary referral hospital	USA	Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10 minutes to max 12mg/hr).	Placebo	MAP	Maternal side effects
<b>Alternative therapies</b>										
Hladunewich 2006 <sup>51</sup>	RCT	Enrolled immediately after birth F/U 10 days	45	29±6 28±7	Tertiary referral hospital	USA	L-arginine 3.5g PO QDS or 10g IV TDS for 3-9 days	Placebo	MAP	Maternal side effects SBP DBP Antihypertensive medication requirement Laboratory values (glomerular filtration rate (GFR) (inulin clearance), Albumin/creatinine (A/C) ratio, vasoactive hormones (NO and cGMP), liver function tests (LFTs), plt) Renal plasma flow (para-amino hippurate clearance), renal blood flow = renal plasma flow / (1-HCT), renovascular resistance = MAP / renal blood flow
Liu 2009 <sup>52</sup>	Quasi-randomised trial	Enrolled day 2 after birth F/U 3 weeks	72	26.6±3.7 25.7±3.9	District general hospital	China <sup>†</sup>	Shengkangbao 10g PO or IV BD for 3 weeks	No intervention	Percentage of cases with positive albuminuria	SBP DBP Laboratory values (24h urinary albumin, plasma total protein, plasma albumin, urinary albumin negative inversion rate, renal function)
<b>Steroids</b>										
Barrilleaux 2005 <sup>53 54</sup>	RCT	Enrolled immediately after birth F/U 4.5 days	157 (175)	24.5±6.8 23.9±6.4	Tertiary referral hospital	USA	Dexamethasone 10mg x 2, then 5mg x 2 IV BD for 48 hours	Placebo	Antihypertensive medication requirement	MAP Critical care admission Length of hospital stay after birth Urine output Laboratory values (plt, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)) Stay in recovery >24h
<b>Atrial natriuretic peptide</b>										
Shigemitsu 2015 <sup>47</sup>	Retrospective cohort study	F/U not specified	16	Not specified	Tertiary referral hospital	Japan	Carperitide (no further details)	Standard care	MAP	Maternal mortality Maternal side effects Need for dialysis Time to diuresis
<b>UTERINE CURETTAGE (8 studies)</b>										
Salvatore 1967 <sup>58</sup>	Prospective cohort study	Enrolled immediately after birth F/U 10 days	48	16-45	Tertiary referral hospital	Brazil <sup>††</sup>	Uterine curettage	No intervention	SBP + DBP	Maternal morbidity (development of pre-eclampsia with severe features – seizures)
Magann 1993 <sup>59</sup>	RCT	Enrolled immediately after birth F/U 24h (telephone at 7 weeks)	32	22.9±5.6 23.4±6.6	Tertiary referral hospital	USA	Uterine curettage	No intervention	MAP	Maternal side effects Length of hospital stay after birth Antihypertensive medication requirement Urine output Laboratory values (HCT, plt, AST, LDH)
Magann 1994 <sup>60</sup>	RCT	Enrolled immediately after birth F/U 48h (telephone at 7 weeks)	45	22.3±6.4 22.8±6.6 22.8±6.1	Tertiary referral hospital	USA	Uterine curettage	(1) Nifedipine PO OR (2) Usual care	MAP	Maternal side effects Urine output Laboratory values (HCT, plt, AST, LDH)
Gocmen 1996 <sup>57</sup>	Prospective cohort study	Enrolled immediately after birth F/U 24h	50	Not specified	Tertiary referral hospital	Turkey <sup>†</sup>	Uterine curettage	No intervention	MAP	Urine output Laboratory values (plt)
Gomez 2005 <sup>61</sup>	RCT	Enrolled immediately after birth F/U not specified	86	Not specified	Tertiary referral hospital	Peru	Uterine curettage	No intervention	MAP	Maternal side effects Length of hospital stay after birth Antihypertensive medication requirement Urine output

Study ID	Methods		Participants			Intervention		Outcomes		
	Study design	Duration	n*	Age (yr) <sup>†</sup>	Setting	Country	Intervention	Control(s)	Primary	Secondary
Alkan 2006 <sup>62</sup>	RCT	Enrolled immediately after birth F/U 24h	56	22.8±3.4 24.6±7.5	Tertiary referral hospital	Turkey	Uterine curettage	No intervention	MAP	Maternal side effects Urine output Laboratory values (plt, LDH, AST, ALT)
Ragab 2013 <sup>15</sup>	RCT	Enrolled immediately after birth F/U 96h	420	Not specified	Tertiary referral hospital	Egypt	Uterine curettage	No intervention	MAP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) MAP (time to MAP ≤105mmHg) Urine output Laboratory values (creatinine, plt, UA)
Mallapur 2015 <sup>18</sup>	RCT	Enrolled immediately after birth F/U 7 days	100	Not specified	Tertiary referral hospital	India	Uterine curettage	No intervention	MAP	Length of hospital stay after birth Urine output Laboratory values (plt, renal and liver function)
<b>ORGANISATION OF CARE (2 studies)</b>										
York 1997 <sup>26</sup>	RCT	Enrolled immediately after birth F/U 8 weeks	96 <sup>§</sup>	28±7 27±7	Tertiary referral	USA	Contact with nurse specialist; early discharge if criteria met; 2 scheduled home visits and 10 telephone calls (twice weekly for 2 weeks, then weekly for 6 weeks) during 8-week F/U	Standard care	Postnatal readmission to secondary care	Functional status Patient satisfaction with care Neonatal rehospitalisation / acute neonatal care Cost
Bibbo 2014 <sup>33</sup>	Retrospective cohort study	F/U not specified (but >7 days)	138	Not specified	Tertiary referral hospital	USA	Specialised postpartum clinic	Usual care	Postnatal readmission to secondary care and triage visits	Primary care provider F/U

<sup>§</sup> Mixture of hypertension and diabetes – unable to separate

**APPENDIX S5: Summary of main results for included studies (n=39)****ANTIHYPERTENSIVE MEDICATIONS (18 studies)****Calcium channel blockers**Study ID: Barton 1990<sup>32</sup>**Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral centres, USA**Intervention:** Nifedipine 10mg PO 4-hourly for 48 hours**Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP (18-24 hours after birth)	Intervention group 93.9±1.6mmHg, control group 100.2±2.6mmHg. Difference 6.3mmHg (p<0.05).	31 (16 intervention, 15 control). Follow-up complete for all participants.	Double-blind RCT. Overall low risk of bias.	

Study ID: Vermillion 1999<sup>21</sup>**Population:** Antenatal and postnatal women with severe pre-eclampsia or super-imposed pre-eclampsia**Setting:** Tertiary referral centres (USA)**Intervention:** Nifedipine 10mg stat PO then 20mg every 20 minutes until BP <160/110mmHg or max 5 doses (90mg) + IV placebo**Comparison:** Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or max 5 doses (300mg) + PO placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP (time to target <160/100mmHg)	Intervention group 25.1±13.6 minutes, control group 43.6±25.4 minutes. Difference 18.5 minutes (p=0.002).	50 (21 postnatal – 10 intervention, 11 control). Follow-up complete for all participants.	Double-blind RCT. Overall high risk of bias (other bias).	Small number of postnatal women (42%) (n<30). Unable to obtain data for postnatal subgroup.

Study ID: Sayin 2005<sup>34</sup>**Population:** Postnatal women with pre-eclampsia, severe pre-eclampsia, superimposed pre-eclampsia or eclampsia**Setting:** Tertiary referral centres (Turkey)**Intervention:** Nifedipine 10mg PO 6-hourly until BP <150/100mmHg for 48 hours**Comparison:** Methyldopa 250mg PO 8-hourly

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP (time to target <150/100mmHg)	Intervention group 6.7±2.5 days; control group 8.6±5.5 days. Difference 1.9 days (NS).	83 (42 intervention, 41 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	

**Vasodilators**Study ID: Palot 1979<sup>36</sup>**Population:** Postnatal women with 'arterial hypertensions of labour and the postpartum period'**Setting:** Not specified (France)**Intervention:** Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose**Comparison:** Clonidine IV and furosemide 20mg IV stat

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
Maternal morbidity (development of pre-eclampsia with severe features)	Intervention group: no women developed eclampsia. Control group: 2 women developed eclampsia. No statistical analysis.	54 (11 intervention, 24 control, 19 non-systematic treatment). Completeness of follow-up not specified.	Retrospective cohort study. Overall high risk of bias (comparability).	No statistical analysis.

Study ID: Griffis 1989<sup>38 39</sup>**Population:** Postnatal women with pre-eclampsia**Setting:** Tertiary referral centres (USA)**Intervention:** Hydralazine 20mg IM 6-hourly for 24h**Comparison:** Methyldopa 250mg IV 6-hourly for 24h

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP (mean at 6 and 12 hours)	6 hours: intervention group 104.5mmHg, control group 112mmHg. Difference 7.5mmHg (p=0.0057). 12 hours: intervention group 100mmHg, control group 108mmHg. Difference 8mmHg (NS).	26 (12 intervention, 14 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	Small sample size (n<30).

Study ID: Walss Rodriguez 1991<sup>40</sup>**Population:** Postnatal women with severe pre-eclampsia**Setting:** Not specified (Mexico)**Intervention:** Hydralazine 40mg PO 6-hourly, duration not specified + if DBP > 110mmHg PRN nifedipine 10mg sublingual every 30 minutes, to maximum of 3 doses (30mg)**Comparison:** Nifedipine 10mg sublingual every 30 minutes if DBP ≥ 110mmHg

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP (mean)	Intervention group 143.6mmHg, control group 138.0mmHg. Difference 5.6mmHg (NS).	38 (18 intervention, 20 control). Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	

Study ID: Begum 2002<sup>17</sup>**Population:** Antenatal and postnatal women with eclampsia**Setting:** Tertiary referral centres (Bangladesh)**Intervention:** Hydralazine 5mg then 2mg IV bolus every 15 minutes until DBP 90-95mmHg**Comparison:** Hydralazine 20mg /200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15 min intervals; until DBP 90-95mmHg

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
DBP (time to target 90-95mmHg)	Intervention group 65.23±23.38 minutes, control group 186.36±79.77 minutes. Difference 121.13 minutes (p<0.001).	77 (15 postnatal – 9 intervention, 6 control). Completeness of follow-up not specified.	Open-label quasi-randomised trial. Overall high risk of bias (multiple domains).	Small number of postnatal women (19%) (n<30). Unable to obtain data for postnatal subgroup.
Study ID: Vigil de Gracia 2007 <sup>35</sup>				
<b>Population:</b> Postnatal women with severe gestational hypertension, severe pre-eclampsia or super-imposed pre-eclampsia				
<b>Setting:</b> Tertiary referral centres (Panama)				
<b>Intervention:</b> Hydralazine 5mg IV every 20 minutes until BP <160/110mmHg or maximum 5 doses				
<b>Comparison:</b> Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or maximum 5 doses (300mg)				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP (persistent hypertension >=160/110mmHg after 5 doses of medication)	Intervention group 0/42, control group 1/40 (NS).	82 (42 intervention, 40 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	
Study ID: Hennessy 2007 <sup>23</sup>				
<b>Population:</b> Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia or essential hypertension				
<b>Setting:</b> Tertiary referral (Australia)				
<b>Intervention:</b> Diazoxide 15mg IV every 3 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 300mg				
<b>Comparison:</b> Hydralazine 5mg IV every 20 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 15mg				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP (proportion achieving target BP <=140/90mmHg)	Intervention group 67%, control group 43% (p<0.01). RR 0.637 (95% CI 0.456-0.89) for not reaching target BP with intervention.	124 total (37 postnatal – 11 intervention, 16 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	Small proportion of postnatal women (30%). Unable to obtain data for postnatal subgroup.
<b>Beta-blockers</b>				
Study ID: Garden 1982 <sup>24</sup>				
<b>Population:</b> Antenatal and postnatal women with severe pre-eclampsia or eclampsia				
<b>Setting:</b> Tertiary referral (South Africa)				
<b>Intervention:</b> Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 160mg/hour				
<b>Comparison:</b> Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 80mg/hour				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
DBP (proportion achieving target DBP 90-100mHg within 2 hours)	Intervention group 5/6, control group 2/6. No statistical analysis.	12 total (6 postnatal – 3 intervention, 3 control). Follow-up complete for all participants.	RCT (blinding not specified). Overall high risk of bias (other bias).	Very small sample size (n<15). Unable to obtain data for postnatal subgroup.
Study ID: Fidler 1982 <sup>42</sup>				
<b>Population:</b> Postnatal women with gestational hypertension				
<b>Setting:</b> Tertiary referral (UK)				
<b>Intervention:</b> Timolol 5mg PO 8-hourly for 9 days				
<b>Comparison:</b> Methyldopa 250mg PO 8-hourly for 9 days				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
DBP (day 1)	Intervention group 88.7mmHg, control group 93.8mmHg. Difference 5.1mmHg (p<0.05).	80 (40 intervention, 40 control). Follow-up complete in 79/80	RCT (blinding not specified). Overall high risk of bias (multiple domains).	
Study ID: Mabie 1987 <sup>22</sup>				
<b>Population:</b> Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia, eclampsia or essential hypertension				
<b>Setting:</b> Tertiary referral (USA)				
<b>Intervention:</b> Labetalol 20mg IV every 10 minutes then escalating until DBP < 100mmHg or maximum cumulative dose reached (300mg)				
<b>Comparison:</b> Hydralazine 5mg IV every 10 minutes until DBP < 100mmHg				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP (mean maximal decrease)	Intervention group 25.5±11.2mmHg, 33.3±13.2mmHg control group. Difference 7.8mmHg (p=0.02).	60 (41 postnatal – 27 intervention, 14 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	
Study ID: Shumard 2016 <sup>41</sup>				
<b>Population:</b> Postnatal women with gestational hypertension or pre-eclampsia				
<b>Setting:</b> Not specified (USA)				
<b>Intervention:</b> Labetalol PO (variable dose and frequency)				
<b>Comparison:</b> Nifedipine PO (variable dose and frequency)				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
Length of hospital stay after delivery	Intervention group 3.5 days, control group 3.6 days. Difference 0.1 days (NS).	128 (42 intervention, 86 control). Follow-up complete for all participants.	Retrospective cohort study. Overall high risk of bias (comparability).	Conference abstract only. Authors did not provide further data.
Study ID: Sharma 2017 <sup>27 28</sup>				
<b>Population:</b> Postnatal women with gestational hypertension or pre-eclampsia				
<b>Setting:</b> Tertiary referral (USA)				
<b>Intervention:</b> Labetalol 200mg PO 12-hourly, increased to 800mg PO 12-hourly as needed				
<b>Comparison:</b> Nifedipine XL 30mg PO once daily, increased to 90mg PO once daily as needed				
Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments

1	SBP + DBP (time to sustained BP control: absence of severe hypertension for $\geq 12$ hours)	Intervention group 37.6 hours, control group 38.2 hours. Difference 0.6 hours (NS).	50 (25 intervention, 25 control). Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	
2	<b>Thiazides</b>				
3	Study ID: Gaisin 2013 <sup>25</sup>				
4	<b>Population:</b> Postnatal women with pre-eclampsia, super-imposed pre-eclampsia or essential hypertension				
5	<b>Setting:</b> Not specified (Russia)				
6	<b>Intervention:</b> Indapamide 1.5mg PO OD, duration unclear				
7	<b>Comparison:</b> Adjusted dose methyldopa				
8	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
9	Systolic and diastolic BP	Intervention group 113 $\pm$ 6/74 $\pm$ 4mmHg, control group 116 $\pm$ 5/75 $\pm$ 4mmHg (NS).	30 (15 intervention, 15 control). Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	Conference abstract only. Authors did not provide further data.
10	Study ID: Gaisin 2014 <sup>37</sup>				
11	<b>Population:</b> Postnatal women with pre-eclampsia				
12	<b>Setting:</b> Not specified (Russia)				
13	<b>Intervention:</b> Indapamide 1.5mg PO once daily + ursodeoxycholic acid 250mg PO three times daily, duration unclear				
14	<b>Comparison:</b> Adjusted dose methyldopa				
15	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
16	SBP + DBP	Intervention group 122 $\pm$ 6/75 $\pm$ 4 mmHg, control group 126 $\pm$ 6/78 $\pm$ 5mmHg (NS).	30 (allocation not described). Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	Conference abstract only. Authors did not provide further data. Number of participants in each group not stated.
17	<b>Indole alkaloids</b>				
18	Study ID: Krebs 1956 <sup>43 44</sup>				
19	<b>Population:</b> Postnatal women with gestational hypertension, pre-eclampsia, severe pre-eclampsia or eclampsia				
20	<b>Setting:</b> Not specified (Germany)				
21	<b>Intervention:</b> Reserpine 0.25mg PO or intramuscular 6-8 hourly for 7 days				
22	<b>Comparison:</b> Phenobarbital				
23	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
24	SBP + DBP (maximal reduction)	Intervention halved time to maximal BP reduction (no further details reported). No statistical analysis.	140 (70 intervention, 70 control). Completeness of follow-up not specified.	Retrospective cohort study. Overall high risk of bias (selection and outcome assessment).	No statistical analysis.
25	<b>Centrally-acting alpha agonists</b>				
26	Study ID: Noronha Neto 2016 <sup>29-31</sup>				
27	<b>Population:</b> Postnatal women with severe hypertensive disorders of pregnancy				
28	<b>Setting:</b> Tertiary referral (Brazil)				
29	<b>Intervention:</b> Clonidine 0.1mg PO repeated every 20 minutes to max 6 doses				
30	<b>Comparison:</b> Captopril 25mg PO repeated every 20 minutes to max 6 doses				
31	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
32	SBP + DBP (episodes $\geq 180$ mmHg and/or DBP $\geq 110$ mmHg)	Intervention group 2.1 $\pm$ 2.1 episodes, control group 3.5 $\pm$ 4.7 episodes (NS).	90 (45 intervention, 45 control). Follow-up complete in 88/90.	Double-blind RCT. Overall low risk of bias.	
33	<b>DIURETICS (4 studies)</b>				
34	Study ID: Matthews 1997 <sup>46</sup>				
35	<b>Population:</b> Postnatal women with severe pre-eclampsia or eclampsia				
36	<b>Setting:</b> Tertiary referral centres (UK)				
37	<b>Intervention:</b> Furosemide 40mg PO once daily for 7 days				
38	<b>Comparison:</b> Placebo				
39	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
40	MAP (decrease)	Intervention group -10.6mmHg, control group -9.75mmHg (NS).	19 (10 intervention, 9 control). Follow-up complete in 18/19.	Double-blind RCT. Overall high risk of bias (other bias).	Small sample size (n<30).
41	Study ID: Ascarelli 2005 <sup>16</sup>				
42	<b>Population:</b> Postnatal women with pre-eclampsia, severe pre-eclampsia or superimposed pre-eclampsia				
43	<b>Setting:</b> Tertiary referral centres (USA)				
44	<b>Intervention:</b> Furosemide 20mg PO once daily + potassium 20mEq PO once daily for 5 days				
45	<b>Comparison:</b> No intervention				
46	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
47	SBP	No significant difference between groups (details not reported). Severe pre-eclampsia (n=70) day 2 SBP intervention group 142 $\pm$ 13mmHg, control group 153 $\pm$ 19mmHg. Difference 11mmHg (p<0.004).	264 (132 intervention, 132 control). Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	
48	Study ID: Amorim 2015 <sup>45</sup>				

1 **Population:** Postnatal women with severe pre-eclampsia  
 2 **Setting:** Tertiary referral (Brazil)  
 3 **Intervention:** Furosemide 40mg PO once daily for maximum 5 days  
 4 **Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP	Intervention group had significantly improved SBP + DBP. Magnitude of difference not reported (p<0.001).	120 (allocation not described). Follow-up complete in 118/120.	Double-blind RCT. Overall high risk of bias (reporting bias).	Conference abstract only. Authors did not provide further data. Number of participants in each group not stated.

8 Study ID: Veena 2017<sup>19</sup>

10 **Population:** Postnatal women with severe pre-eclampsia  
 11 **Setting:** Tertiary referral centre (India)  
 12 **Intervention:** Furosemide 10mg PO once daily plus nifedipine 10mg PO three times daily for 3 days  
 13 **Comparison:** Nifedipine 10mg PO three times daily for 3 days

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP	No significant difference between groups (absolute values and differences not reported, p=0.457 for SBP and p=0.642 for DBP).	100 (50 intervention, 50 control). Follow-up complete in 98/100 (49 intervention, 49 control).	Open-label RCT. Overall high risk of bias (multiple domains).	

#### 18 OTHER DRUGS (7 studies)

##### 19 Selective 5-HT antagonists

21 Study ID: Weiner 1982<sup>48</sup>

22 **Population:** Postnatal women with severe pre-eclampsia  
 23 **Setting:** Tertiary referral (USA)  
 24 **Intervention:** R41468 IV (dose not specified) bolus then infusion for 90 minutes  
 25 **Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP (mean maximal decline)	Intervention group 31.6mmHg, control group 6.0mmHg. Difference 25.6mmHg (p<0.001).	5 (crossover). Follow-up complete in all participants.	Double blind RCT (crossover). Overall high risk of bias (other bias).	Conference abstract only. Authors did not provide further data. Very small sample size (n<15).

29 Study ID: Weiner 1984<sup>49</sup>

31 **Population:** Postnatal women with pre-eclampsia and super-imposed pre-eclampsia  
 32 **Setting:** Tertiary referral (USA)  
 33 **Intervention:** Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5 minutes if no response.  
 34 **Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
SBP + DBP (mean maximal decline)	Intervention group 41/34mmHg, control group 7/7mmHg. Difference 34/27mmHg (p<0.001).	20 (crossover). Follow-up complete in all participants.	Double blind RCT (crossover). Overall high risk of bias (other bias).	Small sample size (n<30).

38 Study ID: Montenegro 1985<sup>50</sup>

39 **Population:** Postnatal women with pre-eclampsia  
 40 **Setting:** Tertiary referral (USA)  
 41 **Intervention:** Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10 minutes to max 12mg/hr).  
 42 **Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	Intervention group had significantly improved MAP, over 30 minutes after drug administered. F = 9.66 (p <0.01)	30 (crossover). Follow-up complete in 23/30.	Double blind RCT (crossover). Overall high risk of bias (multiple domains).	

#### 46 Alternative therapies

48 Study ID: Hladunewich 2006<sup>51</sup>

49 **Population:** Postnatal women with pre-eclampsia  
 50 **Setting:** Tertiary referral (USA)  
 51 **Intervention:** L-arginine 3.5g PO four times daily OR L-arginine 10g IV three times daily (if unable to take PO) for 3-9 days postpartum  
 52 **Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	Intervention group day 3 102±12 mmHg and day 10 98±14 mmHg; control group day 3 103±12mmHg and day 10 96±11 mmHg. Difference day 3 1mmHg, day 10 2mmHg (NS).	45 (22 intervention, 23 control). Follow-up complete in 39/45.	Double blind RCT. Overall high risk of bias (multiple domains).	

57 Study ID: Liu 2009<sup>52</sup>

58 **Population:** Postnatal women with severe pre-eclampsia  
 59 **Setting:** District general (China)  
 60 **Intervention:** Shengkangbao 10g PO or IV twice daily for 3 weeks  
 60 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
-----------------	------------------	------------------------	-------------------------	----------

1	Percentage of cases with positive albuminuria	At 3 weeks intervention group 0.7+/-0.8% positive albuminuria, control group 1.5+/-0.9%. Difference 0.8% (p<0.01).	77 (allocation not described). Follow-up complete in 72 (38 intervention, 32 control)	Open-label quasi-randomised study. Overall high risk of bias (multiple domains).	Clinical significance of primary outcome unclear.
2	<b>Steroids</b>				
3	Study ID: Barrilleaux 2005 <sup>53,54</sup>				
4	<b>Population:</b> Postnatal women with severe pre-eclampsia and eclampsia				
5	<b>Setting:</b> Tertiary referral (USA)				
6	<b>Intervention:</b> Dexamethasone 10mg x2, then 5mg x 2 IV 12-hourly for 48 hours				
7	<b>Comparison:</b> Placebo (IV saline)				
8	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
9	Anti-hypertensive medication requirement	Intervention group 38/77, control group 31/80 required antihypertensive treatment in the first 48h PN (NS).	157 (77 intervention, 80 control). Follow-up complete in 155/157.	Double blind RCT. Overall high risk of bias (reporting bias).	
10	<b>Atrial natriuretic peptide</b>				
11	Study ID: Shigemitsu 2015 <sup>47</sup>				
12	<b>Population:</b> Postnatal women with severe pre-eclampsia, HELLP syndrome or placental abruption				
13	<b>Setting:</b> Tertiary referral (Japan)				
14	<b>Intervention:</b> Carperitide (no further details supplied)				
15	<b>Comparison:</b> No intervention				
16	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
17	MAP	Intervention group had significantly improved MAP at 48 hours. Magnitude of difference not reported, no p value presented.	16 (6 intervention, 10 control) Follow-up complete for all participants.	Retrospective cohort study. Overall high risk of bias (comparability).	Conference abstract only. Authors did not provide further data. Small sample size (n<30)
18	<b>UTERINE CURETTAGE (8 studies)</b>				
19	Study ID: Salvatore 1967 <sup>58</sup>				
20	<b>Population:</b> Postnatal women with severe pre-eclampsia or eclampsia				
21	<b>Setting:</b> Tertiary referral (Brazil)				
22	<b>Intervention:</b> Uterine curettage				
23	<b>Comparison:</b> No intervention				
24	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
25	SBP + DBP (proportion achieving target <140/90mmHg)	24 hours: intervention group 45%, control group 11%. No statistical analysis. 48 hour: intervention group 70%, control group 29%. No statistical analysis.	48 (20 intervention, 28 control) Follow-up complete for all participants.	Prospective cohort study. Overall high risk of bias (comparability).	Significant differences in study group populations (9/20 intervention group eclamptic at enrolment, 28/28 control group).
26	Study ID: Magann 1993 <sup>59</sup>				
27	<b>Population:</b> Postnatal women with severe pre-eclampsia				
28	<b>Setting:</b> Tertiary referral (USA)				
29	<b>Intervention:</b> Uterine curettage				
30	<b>Comparison:</b> No intervention				
31	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
32	MAP	Intervention group had significantly improved MAP to 24 hours after birth. Difference 6-10mmHg (most significant at 16 hours p<0.0002).	32 (16 intervention, 16 control). Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	
33	Study ID: Magann 1994 <sup>60</sup>				
34	<b>Population:</b> Postnatal women with severe pre-eclampsia				
35	<b>Setting:</b> Tertiary referral (USA)				
36	<b>Intervention:</b> Uterine curettage				
37	<b>Comparison:</b> Oral nifedipine OR no intervention				
38	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
39	MAP	Intervention group had significantly improved MAP 8-48 hours after birth. Difference 9-13mmHg (p=0.0017). No difference between curettage and nifedipine.	45 (15 intervention, 15 each control group) Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	
40	Study ID: Goemen 1996 <sup>57</sup>				
41	<b>Population:</b> Postnatal women with pre-eclampsia				
42	<b>Setting:</b> Tertiary referral (Turkey)				
43	<b>Intervention:</b> Uterine curettage				
44	<b>Comparison:</b> No intervention				
45	<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>	<b>Comments</b>
46	MAP	Intervention group had significantly improved MAP to 24 hours after birth. Magnitude of difference not reported (p=0.01).	50 (30 intervention, 20 control) Completeness of follow-up not specified.	Prospective cohort study. Overall high risk of bias (comparability and outcome assessment).	Conference abstract only. Authors did not provide further data.
47	Study ID: Gomez 2005 <sup>61</sup>				

1 **Population:** Postnatal women with severe pre-eclampsia

2 **Setting:** Tertiary referral (Peru)

3 **Intervention:** Uterine curettage

4 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	Intervention group had significantly improved MAP. Time point not specified. Magnitude of difference not reported (p<0.001).	86 (27 intervention, 59 control) Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	Conference abstract only. Authors did not provide further data.

8 Study ID: Alkan 2006<sup>62</sup>

9 **Population:** Postnatal women with severe pre-eclampsia

10 **Setting:** Tertiary referral (Turkey)

11 **Intervention:** Uterine curettage

12 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	24 hours: Intervention group 103.4±7.8 mmHg, control group 110.2±4.8. Difference 6.8mmHg (p<0.05).	56 (31 intervention, 25 control) Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	

16 Study ID: Ragab 2013<sup>15</sup>

17 **Population:** Postnatal women with severe pre-eclampsia or eclampsia

18 **Setting:** Tertiary referral (Egypt)

19 **Intervention:** Uterine curettage

20 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	6 hours: Intervention group 140.1±6.12 mmHg, control group 152.4±3.7 mmHg. Difference 12.3mmHg (p=0.02). 24 hours: Intervention group 101.4±7.14 mmHg, control group 110.6±2.22 mmHg. Difference 9.2mmHg (p=0.01).	420 (220 intervention, 200 control) Follow-up complete for all participants.	Open-label RCT. Overall high risk of bias (multiple domains).	

26 Study ID: Mallapur 2015<sup>18</sup>

28 **Population:** Postnatal women with severe pre-eclampsia or eclampsia

29 **Setting:** Tertiary referral (India)

30 **Intervention:** Uterine curettage

31 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
MAP	From 4 hours after birth: Intervention group 116±4.4 mmHg, control group 123.6±6.1 mmHg. Difference 7.6mmHg (p<0.001).	100 (50 intervention, 50 control) Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	Conference abstract only. Authors did not provide further data.

### 35 ORGANISATION OF CARE (2 studies)

36 Study ID: York 1997<sup>26</sup>

38 **Population:** Postnatal women with pre-eclampsia or essential hypertension, or diabetes

39 **Setting:** Tertiary referral (USA)

40 **Intervention:** Nurse specialist follow-up

41 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
Postnatal readmission to secondary care	No significant difference between groups.	96 (44 intervention, 52 control) Completeness of follow-up not specified.	Open-label RCT. Overall high risk of bias (multiple domains).	Population mixed diabetes and/or hypertension – unable to separate.

45 Study ID: Bibbo 2014<sup>33</sup>

46 **Population:** Postnatal women with pre-eclampsia

47 **Setting:** Tertiary referral (USA)

48 **Intervention:** Specialised postpartum clinic

49 **Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence	Comments
Postnatal readmission to secondary care and triage visits	Intervention group 21.7%; control group 8.7% (p<0.039)	138 (69 intervention, 69 control) Completeness of follow-up not specified.	Retrospective cohort study. Overall high risk of bias (comparability).	Conference abstract only. Authors did not provide further data.



**Appendix S6: Risk of bias in included studies (n=38)****Appendix S6a: Risk of bias in included RCTs and quasi-randomised studies (n=31)**

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
<b>ANTIHYPERTENSIVE MEDICATIONS</b>							
Fidler 1982 <sup>42</sup>	Unclear	Unclear	Unclear	Unclear	High	High	Low
Garden 1982 <sup>24</sup>	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Mabie 1987 <sup>22</sup>	Unclear	Unclear	High	High	Low	Low	High
Griffis 1989 <sup>38 39</sup>	Unclear	Low	High	High	High	High	High
Barton 1990 <sup>32</sup>	Low	Low	Low	Low	Low	Low	Low
Walss Rodriguez 1991 <sup>40</sup>	Low	Low	High	High	Unclear	Unclear	Low
Vermillion 1999 <sup>21</sup>	Low	Low	Low	Low	Low	Low	High
Begum 2002 <sup>17</sup>	High	High	High	High	Unclear	Unclear	High
Sayin 2005 <sup>34</sup>	Unclear	Unclear	High	High	Low	Unclear	High
Hennessy 2007 <sup>23</sup>	Unclear	Low	High	High	Low	Low	High
Vigil-de-Gracia 2007 <sup>35</sup>	Low	Low	High	High	Low	Low	Low
Gaisin 2013 <sup>25</sup>	Unclear	Unclear	High	High	Unclear	High	High
Gaisin 2014 <sup>37</sup>	Unclear	Unclear	High	High	Unclear	Unclear	High
Noronha Neto 2016 <sup>29-31</sup>	Low	Low	Low	Unclear	Low	Low	Low
Sharma 2017 <sup>27 28</sup>	Low	Low	High	High	Unclear	Low	Low
<b>DIURETICS</b>							
Matthews 1997 <sup>46</sup>	Unclear	Low	Low	Low	Low	Unclear	High
Ascarelli 2005 <sup>16</sup>	Unclear	Low	High	High	Unclear	High	Low
Amorim 2015 <sup>45</sup>	Low	Low	Low	Low	Low	High	Low
Veena 2017 <sup>19</sup>	Low	Low	High	High	Unclear	Unclear	Unclear
<b>OTHER DRUGS</b>							
Weiner 1982 <sup>48</sup>	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Weiner 1984 <sup>49</sup>	Low	Unclear	Low	Low	Low	Unclear	High
Montenegro 1985 <sup>50</sup>	Unclear	Unclear	Low	Low	High	High	High
Barrilleaux 2005 <sup>53 54</sup>	Low	Low	Low	Low	Low	High	High
Hladunewich 2006 <sup>51</sup>	Low	Low	Low	Low	High	High	High
Liu 2009 <sup>52</sup>	High	High	High	High	High	Unclear	High
<b>UTERINE CURETTAGE</b>							
Magann 1993 <sup>59</sup>	Low	Low	High	High	Unclear	Unclear	Low
Magann 1994 <sup>60</sup>	Low	Unclear	High	High	Unclear	Unclear	Low
Gomez 2005 <sup>61</sup>	Unclear	Unclear	High	High	Unclear	High	Low
Alkan 2006 <sup>62</sup>	Unclear	Unclear	High	High	Low	High	High
Ragab 2013 <sup>15</sup>	Low	Low	High	High	Low	Low	Low
Mallapur 2015 <sup>18</sup>	Low	Unclear	High	High	Unclear	Unclear	High
<b>ORGANISATION OF CARE</b>							
York 1997 <sup>26</sup>	Unclear	Low	High	High	Unclear	Unclear	High

## Appendix S6b: Risk of bias in included cohort studies (n=7)

Study ID	Selection				Comparability <sup>1</sup>	Outcome		
	Representative-ness <sup>2</sup>	Selection of non-exposed <sup>3</sup>	Ascertainment of exposure <sup>4</sup>	Outcome of interest not present at start		Assessment <sup>5</sup>	F/U long enough	Adequacy of F/U <sup>6</sup>
<b>ANTIHYPERTENSIVE MEDICATIONS</b>								
Krebs 1956 <sup>43 44</sup>	Low (a)	Low (a)	Unclear (d)	Low (Yes)	Low (a)	High (b)	Low (Yes)	Unclear (d)
Palot 1979 <sup>36</sup>	Unclear (d)	Low (a)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)
Shumard 2016 <sup>41</sup>	Low (a)	Low (a)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
<b>OTHER DRUGS</b>								
Shigemitsu 2015 <sup>47</sup>	Unclear (d)	Unclear (c)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Unclear (d)
<b>UTERINE CURETTAGE</b>								
Salvatore 1967 <sup>58</sup>	High (b)	High (b)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
Gocmen 1996 <sup>57</sup>	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	High (No)	Unclear (d)
<b>ORGANISATION OF CARE</b>								
Bibbo 2014 <sup>33</sup>	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)

<sup>1</sup> (a) study controls for most important factor; (b) study controls for any additional factor

<sup>2</sup> (a) truly representative of the average in the community; (b) somewhat representative of the average in the community; (c) selected group of users e.g. nurses, volunteers; (d) no description of the derivation of the cohort

<sup>3</sup> (a) drawn from the same community as the exposed cohort; (b) drawn from a different source; (c) no description of the derivation of the non-exposed cohort

<sup>4</sup> (a) secure record (e.g. surgical record); (b) structured interview; (c) written self-report; (d) no description

<sup>5</sup> (a) independent blind assessment; (b) record linkage; (c) self-report; (d) no description

<sup>6</sup> (a) complete follow-up; (b) subjects lost to follow-up unlikely to introduce bias (>90% follow-up rate); (c) follow up rate <90% and no description of those lost; (d) no statement

# BMJ Open

## Postpartum management of hypertensive disorders of pregnancy: a systematic review

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Manuscripts

# 1 Postpartum management of hypertensive disorders of 2 pregnancy: a systematic review

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21 **Short title:** Postnatal Hypertension Management

22 **Competing interests statement:** None of the authors has any conflicts of interest to declare.

## 23 **Abstract**

### 24 **Objectives**

25 Hypertensive disorders of pregnancy (HDP) affect one in ten pregnancies and often persist  
26 postpartum when complications can occur. We aimed to determine the effectiveness and  
27 safety of pharmacologic interventions, other interventions, and different care models for  
28 postpartum hypertension management.

### 29 **Design**

30 A systematic review was undertaken. Nine electronic databases, including Medline, were  
31 searched from inception to 16/03/2017. After duplicate removal, 4,561 records were  
32 screened. Two authors independently selected studies, extracted study characteristics and  
33 data, and assessed methodological quality.

### 34 **Setting**

35 Randomised controlled trials, case-control studies, and cohort studies from any country and  
36 healthcare setting.

### 37 **Participants**

38 Postnatal women with HDP.

### 39 **Interventions**

40 Therapeutic intervention for management of hypertension, compared with another  
41 intervention, placebo, or no intervention.

### 42 **Primary and secondary outcome measures**

43 Outcome data were collected for maternal mortality and severe morbidity; systolic, diastolic  
44 and mean arterial blood pressure (BP) control; and safety data. Secondary outcome data  
45 collected included the length of postnatal hospital stay and laboratory values.

### 46 **Results**

47 39 studies were included (n=2,901). Results were heterogeneous in terms of intervention,  
48 comparison and outcome requiring a narrative approach. There were insufficient data to  
49 recommend any single pharmacologic intervention. 18 studies reported calcium-channel  
50 blockers, vasodilators and beta-blockers lowered BP postpartum. 12 of these reported safety  
51 data. Limited data existed regarding management in the weeks following hospital discharge.  
52 Neither loop diuretics (three studies) nor corticosteroids (one study) produced clinical benefit.

1  
2  
3 53 Uterine curettage significantly reduced BP over the first 48 hours postpartum (range 6-  
4 54 13mmHg) compared to standard care (eight studies), with safety data only reported by 4/8  
5 55 studies.  
6  
7

## 8 9 56 **Conclusion**

10 57 There was insufficient evidence to recommend a particular BP threshold, agent, or model of  
11 58 care but three classes of antihypertensive appeared variably effective. Further comparative  
12 59 research, including robust safety data, is required. Curettage reduced BP, but without  
13 60 adequate reporting of harms, so cannot currently be recommended.  
14  
15  
16  
17

## 18 19 61 **Strengths and limitations of this study**

- 20 62 • All types of intervention for the management of postpartum hypertension – medical,  
21 63 surgical and organisation of care – were eligible for inclusion in this review.  
22  
23  
24 64 • Randomised controlled studies plus other experimental study designs (cohort studies,  
25 65 case-control studies and quasi-randomised studies) were included and no limitations  
26 66 were imposed in terms of language or publication date, resulting in a comprehensive  
27 67 review.  
28  
29  
30 68 • This review highlights significant evidence gaps, demonstrating that further  
31 69 comparative research is required, particularly to clarify postpartum antihypertensive  
32 70 selection.  
33  
34 71 • Although 39 studies were included, the majority had a high risk of bias such that the  
35 72 evidence provided by this review is of low quality.  
36  
37  
38 73 • The 39 studies reported a broad range of heterogeneous outcomes, limiting  
39 74 meaningful comparison.  
40  
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46

## 47 75 **Keywords**

48 76 Preeclampsia, gestational hypertension, postpartum, hypertensive disorders of pregnancy,  
49 77 antihypertensive medication, systematic review  
50  
51  
52

## 53 54 78 **Abbreviations**

55 79 BP Blood pressure  
56  
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- 1  
2  
3 80 HDP Hypertensive disorders of pregnancy  
4  
5 81 MAP Mean arterial pressure  
6  
7  
8 82 NICE National Institute of Health and Care Excellence  
9  
10 83 RCT Randomised controlled trial  
11  
12 84 SSRI Selective serotonin reuptake inhibitor  
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14  
15 85  
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18  
19  
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21  
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## 86 **Introduction**

87 Hypertensive disorders of pregnancy (HDP) often persist following delivery,<sup>1</sup> and  
88 occasionally arise de novo postpartum.<sup>2</sup> In both scenarios adverse events can occur during  
89 this period. Approximately one-third of eclampsia occurs postpartum, nearly half beyond 48  
90 hours after childbirth.<sup>3-5</sup> Half of the women who sustain an intracerebral haemorrhage in  
91 association with preeclampsia do so following birth.<sup>6</sup> Women may enter the postnatal period  
92 requiring large doses of antihypertensive medication, but the majority will be treatment-free  
93 by three to six months.<sup>1 7</sup> This rapidly changing blood pressure (BP) poses a challenge in  
94 terms of appropriate antihypertensive selection and dose adjustment.

95 The National Institute for Health and Care Excellence (NICE) recommends frequent  
96 postnatal BP monitoring for women with both preeclampsia (every one to two days for two  
97 weeks) and gestational hypertension (at least once between day three and five).<sup>8</sup> The  
98 guideline stipulates thresholds for the increase or commencement ( $\geq 150/100$ mmHg) and the  
99 reduction or cessation (consider  $< 140/90$ mmHg and reduce  $< 130/80$ mmHg) of  
100 antihypertensive medication after birth. However, little detail is provided about frequency or  
101 proportion of dose reduction or how to manage multiple medications.<sup>8</sup> The American College  
102 of Obstetricians and Gynecologists recommend that BP be monitored in hospital (or with an  
103 equivalent level of outpatient surveillance) for 72 hours after birth, and checked again seven  
104 to ten days postpartum (sooner if a woman is symptomatic).<sup>9</sup> In line with NICE, they propose  
105 treating BP when  $\geq 150/100$ mmHg, but add this should be on two measures, four to six hours  
106 apart. They make no suggestion regarding BP thresholds for medication reduction, implying  
107 uncertainty about when to decrease or stop treatment.

108 A Cochrane review (search date January 2013) evaluated medical interventions for  
109 prevention and treatment of postnatal hypertension. This was limited to randomised  
110 controlled trials (RCTs) and included only nine studies.<sup>10</sup> Given the paucity of evidence  
111 available, due to Cochrane's restriction to randomised trials alone, we have undertaken an  
112 updated systematic review of the postpartum management of hypertension in women with  
113 HDP with a broader scope: including the full range of interventions studied, and  
114 incorporating cohort and case-control studies, alongside RCTs. Our specific questions were:  
115 [1] How should BP be monitored in women with HDP postpartum? [2] What BP thresholds  
116 should be used for antihypertensive treatment initiation, adjustment and cessation  
117 postpartum? [3] Which antihypertensive medication(s) should be used in postpartum in



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2  
3 118 women with HDP? [4] What are the benefits and harms of other therapeutic interventions for  
4  
5 119 women with HDP postpartum?  
6  
7

## 8 **Material and methods**

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10 121 A protocol, with explicitly defined objectives, study selection criteria, and approaches to  
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12 122 assessing study quality, outcomes and statistical methods, was developed (Appendix S1).  
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14 123 This was registered with PROSPERO: International Prospective Register of Systematic  
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16 124 Reviews (CRD42015015527) and is available online  
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18 125 ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015015527](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527)). We  
19  
20 126 followed the guidelines for meta-analyses and systematic reviews outlined by the Preferred  
21  
22 127 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix  
23  
24 128 S2).<sup>11</sup>

25  
26 129 A systematic literature review was undertaken to capture evidence from human studies  
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28 130 regarding postpartum hypertension management in women with HDP, without restriction by  
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30 131 language or publication date (Appendix S1). We searched the following databases, from  
31  
32 132 inception to 16/03/2017: Cochrane Database of Systematic Reviews (CDSR), Database of  
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34 133 Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials  
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36 134 (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL),  
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38 135 Embase, Medline, PsycINFO, Science Citation Index, Science (Web of Science Core  
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40 136 Collection), Social Science Citation Index & Conference Proceedings Citation Index. We  
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42 137 hand-searched reference lists and contacted relevant experts for potentially relevant studies,  
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44 138 which might have been missed by electronic searches.<sup>12</sup>

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46 139 We included RCTs, quasi-randomised studies, case-control studies, prospective and  
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48 140 retrospective cohort studies, assessing interventions for hypertension management  
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50 141 postpartum in women with HDP (gestational hypertension, pre-eclampsia, chronic  
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52 142 hypertension and super-imposed pre-eclampsia) arising both during pregnancy and de novo  
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54 143 in the postnatal period. Consistent with guidance from Cochrane, conference abstracts were  
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56 144 included.<sup>5</sup>

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58 145 Two reviewers (AC/LP) independently screened the titles and abstracts, and then critically  
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60 146 reviewed the full text of selected studies to assess eligibility. Discrepancies were resolved by  
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148 147 discussion before independent extraction of relevant data by the two reviewers. For trials with  
multiple intervention arms, we extracted data from eligible comparison arms. Data were

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3 149 extracted for the primary and secondary outcomes outlined in Table 1. Due to the  
4 150 heterogeneous nature of these studies, a narrative synthesis was undertaken.

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7 151 Two reviewers (AC/LP) independently assessed each trial's methodological quality using the  
8 152 Cochrane Collaboration's tool for assessing the risk of bias in RCTs,<sup>13</sup> and the Newcastle-  
9 153 Ottawa scale for case-control and cohort studies.<sup>14</sup> A global assessment of bias across trials  
10 154 was made.

## 15 155 **Results**

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17 156 Our searches yielded 7,105 records and after excluding duplicates, 4,561 titles and abstracts  
18 157 were screened (Figure 1). 80 full-text articles were assessed: 35 articles were excluded  
19 158 (Appendix S3). 45 articles, representing 39 studies (32 randomised trials, two prospective  
20 159 cohort studies, and five retrospective cohort studies) reporting data from 2,901 postnatal  
21 160 participants met our inclusion criteria (Appendix S4). 9/39 (23%) were published only as  
22 161 conference abstracts. No further details were made available following author contact.

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28 162 A range of interventions was assessed including antihypertensive medications (18 studies,  
29 163 n=982), loop diuretics (four studies, n=503), parenteral steroids (one study, n=157), other  
30 164 medications (six studies, n=188), uterine curettage (eight studies, n=837) and novel models of  
31 165 care (two studies, n=234). 9/39 (23%) included  $\geq 100$  participants, and only two studies  
32 166 included  $\geq 200$  participants.<sup>15 16</sup> Four were from lower-middle-income settings<sup>15 17-19</sup>  
33 167 (classified according to the United Nations<sup>20</sup>), and 13/39 (33%) studies had follow-up periods  
34 168 longer than seven days (Appendix S4). Only 5/39 (13%) and 7/39 (18%) studies,  
35 169 respectively, reported maternal mortality or major maternal morbidity, and whilst the  
36 170 majority of studies did report some measure of BP control, three did not (Tables 2a&b).  
37 171 19/39 (49%) studies reported safety data (Tables 2a&b).

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45 172 5/39 (13%) studies (all evaluating antihypertensive medications) involved mixed antenatal  
46 173 and postnatal populations<sup>17 21-24</sup>. Authors were contacted to request their dataset for the  
47 174 postnatal participants, but no data were made available. 6/39 (15%) studies included  
48 175 participants with chronic hypertension alongside women with de novo HDP (gestational  
49 176 hypertension or pre-eclampsia).<sup>22 23 25-31</sup> 12/39 (31%) studies included women with eclampsia  
50 177 – in one all participants were eclamptic (Appendix S5).<sup>17</sup>

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56 178 30/32 (94%) included RCTs were judged to be at high overall risk of bias, by both reviewers,  
57 179 according to the Cochrane tool, 23/32 (72%) for multiple domains. Only 2/32 (6%) were

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3 180 thought to be clearly at low risk of bias.<sup>29-32</sup> All included cohort studies were deemed to have  
4 181 a high risk of bias in at least one domain of the Newcastle-Ottawa scale (Appendix S6).

7 182 **How should blood pressure be monitored postpartum in women with hypertensive**  
8 183 **disorders of pregnancy?**

10 184 No studies specifically addressed the frequency or method of postnatal BP monitoring. Two  
11 185 evaluated the impact of postpartum care organisation (n=234), using the postnatal  
12 186 readmission rate as their primary outcome (Appendix S4). Neither reported maternal  
13 187 mortality or morbidity, safety data nor any measure of BP control (Table 2b).<sup>26 33</sup>

17 188 One assessed introduction of a specialised postpartum clinic (no further details were given)  
18 189 and demonstrated an increased postnatal readmission and triage visit rate (22% intervention  
19 190 group, 9% control group: difference 13%,  $p<0.04$ ) although 86% occurred before a  
20 191 participant was seen in the clinic.<sup>33</sup> The second study evaluated specialist nurse follow-up,  
21 192 including home visits and telephone contact, and reported no significant difference in the  
22 193 postnatal readmission rate compared to standard care.<sup>26</sup>

28 194 **What blood pressure thresholds should be used for antihypertensive treatment**  
29 195 **initiation, adjustment and cessation postpartum?**

30 196 No relevant studies identified.

34 197 **Which antihypertensive medication(s) should be used postpartum in women with**  
35 198 **hypertensive disorders of pregnancy?**

36 199 14 randomised trials (n=645), one quasi-randomised trial (n=15), and three retrospective  
37 200 cohort studies (n=322) evaluated antihypertensive medications (Appendix S4). Only three  
38 201 studies reported maternal mortality,<sup>29-31 34 35</sup> and three reported maternal morbidity: no  
39 202 differences between groups were reported (Table 2a).<sup>29-31 35 36</sup> 12 studies reported safety data,  
40 203 in comparisons between multiple classes of antihypertensive agents (Table 2a): no clear  
41 204 differences were established, although one study found a greater number of minor side effects  
42 205 reported with oral nifedipine than with oral labetalol.<sup>27 28</sup>

49 206 The vast majority of included studies evaluated either acute control of severe hypertension  
50 207 (7/18, 39%), or BP control in the few days after delivery, whilst women remained hospital  
51 208 inpatients (8/18, 44%). Only three studies, two published only as conference abstracts,  
52 209 evaluated BP control in the weeks and months following hospital discharge.<sup>25 27 28 37</sup>

### 210 **Calcium-channel blockers**

211 Three small studies examined oral nifedipine (n=135): nifedipine resulted in a greater  
212 decrease in MAP 18-24 hours after childbirth than placebo (intervention group  
213 93.9±1.6mmHg, control group 100.2±2.6mmHg, difference 6.3mmHg,  $p<0.05$ ), but not at  
214 other time points to 48 hours (one RCT, n=31).<sup>32</sup> Nifedipine controlled severe hypertension  
215 to <160/100mmHg more quickly than labetalol (intervention group 25.1±13.6 minutes,  
216 control group 43.6±25.4 minutes: difference 18.5 minutes,  $p=0.002$ ; one RCT, n=21).<sup>21</sup> A  
217 single RCT (n=83), reported no significant difference in time taken to control BP to  
218 <150/100mmHg when comparing nifedipine with methyldopa.<sup>34</sup>

### 219 **Vasodilators**

220 Six studies looked at the use of vasodilators (n=252). All utilised hydralazine via a range of  
221 administration routes. Bolus intravenous hydralazine controlled severe hypertension more  
222 quickly than continuous infusion (intervention group 65.23±23.38 minutes, control group  
223 186.36±79.77 minutes: difference -121.13 minutes,  $p<0.001$ ); one quasi-randomised study,  
224 n=15 (postnatal)).<sup>17</sup> Intramuscular hydralazine produced a more significant improvement in  
225 MAP at six hours than intravenous methyldopa (intervention group 104.5mmHg, control  
226 group 112mmHg: difference -7.5mmHg  $p=0.0057$ ) but not at other time points to 24 hours  
227 (one RCT, n=26).<sup>38 39</sup> There was no difference in BP control when comparing oral  
228 hydralazine with oral nifedipine (one RCT, n=38), or intravenous labetalol (one RCT,  
229 n=82).<sup>35 40</sup>

230 Bolus diazoxide was significantly more effective in achieving a target BP of  $\leq 140/90$ mmHg  
231 than intravenous hydralazine (intervention group 67%, control group 43%: RR 0.64, 95% CI  
232 0.46-0.89; one RCT, n=37 (postnatal)).<sup>23</sup> One retrospective cohort study did not present any  
233 statistical analysis.<sup>36</sup>

### 234 **Beta-blockers**

235 Five studies assessed the efficacy of beta-blockers (four RCTs and one retrospective cohort  
236 study, n=305). Two RCTs compared intravenous labetalol with intravenous  
237 hydralazine/dihydralazine: one involved only six postnatal women and presented no  
238 statistical analysis of the data.<sup>24</sup> The other found a significantly greater mean maximal  
239 decrease in MAP with intravenous labetalol (intervention group 25.5±11.2mmHg, control  
240 group 33.3±13.2mmHg: difference -7.8mmHg,  $p=0.02$ ; one RCT, n=32 (postnatal)).<sup>22</sup>  
241 Results conflicted regarding whether oral labetalol was more or less effective than oral

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3 242 nifedipine: a cohort study reported that labetalol controlled BP less rapidly than nifedipine  
4 243 (intervention group 2.7 days, control group 1.7 days: difference 1.0 days,  $p=0.0031$ ; one  
5 244 retrospective cohort study,  $n=128$ ).<sup>41</sup> However, this result was not replicated by an RCT,  
6 245 where the time to BP control was similar in the two groups ( $n=50$ ).<sup>27 28</sup> Neither study  
7 246 demonstrated a difference in the postnatal length of stay ( $n=178$ ). Timolol was effective in  
8 247 decreasing diastolic BP on day one postnatal when compared with methyldopa (intervention  
9 248 group 88.7mmHg, control group 93.8mmHg: difference -5.1mmHg;  $p<0.05$ ; one RCT,  
10 249  $n=80$ ).<sup>42</sup>

### 17 250 *Other antihypertensive medications*

18 251 No statistically significant difference was found between oral clonidine and oral captopril in  
19 252 the incidence of episodes of severe hypertension postpartum (one RCT,  $n=90$ ).<sup>29-31</sup> Two  
20 253 RCTs evaluating indapamide versus methyldopa found no difference in BP control over 6-12  
21 254 months postpartum ( $n=60$ ).<sup>25 37</sup> One retrospective cohort study ( $n=140$ ) compared reserpine  
22 255 with phenobarbital: the results suggested that reserpine might achieve faster and greater BP  
23 256 reduction (data extracted from graphs; no statistical analysis). No adverse events were  
24 257 reported in the intervention group.<sup>43 44</sup>

### 31 258 **What are the benefits and harms of other therapeutic interventions for women with** 32 259 **hypertensive disorders of pregnancy postpartum?**

#### 35 260 *Loop Diuretics*

36 261 Four RCTs ( $n=503$ ) examined loop diuretics versus placebo or usual care in postpartum  
37 262 hypertension management in women with HDP. None reported maternal mortality or safety  
38 263 data. Only two reported major maternal morbidity, neither demonstrating a difference  
39 264 between groups (Table 2b).<sup>16 19</sup>

40 265 One RCT ( $n=120$ ) reported significant improvement in the primary outcome of mean systolic  
41 266 and diastolic BP with oral furosemide versus placebo (magnitude of difference or time points  
42 267 of measurements not stated,  $p<0.001$ ).<sup>45</sup> This was not the case in the other placebo-controlled  
43 268 RCT, which found no significant difference ( $n=19$ ).<sup>46</sup> Two further RCTs ( $n=364$ ) found no  
44 269 significant difference in BP control with oral furosemide versus usual care.<sup>16 19</sup> In one of  
45 270 these, subgroup analysis of women with severe preeclampsia ( $n=70$ ) found women who  
46 271 received oral furosemide had a significantly lower systolic BP day 2 postpartum (intervention  
47 272 group  $142\pm 13$ mmHg, control group  $153\pm 19$ mmHg: difference -11mmHg,  $p<0.004$ ), but not  
48 273 at other time points.<sup>16</sup> In the other trial ( $n=100$ ), furosemide reduced the need for additional

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3 274 antihypertensive treatment during the three days of therapy (intervention group 8.0%, control  
4 275 group 26.0% difference 18%,  $p=0.017$ ), but this difference did not persist to hospital  
5 276 discharge.<sup>19</sup>  
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9 277 **Other drugs**

10 278 Five RCTs, one quasi-randomised study and one retrospective cohort study investigated the  
11 279 utility of different drug classes in HDP postpartum (Appendix S5). Three studies reported  
12 280 safety data, but only one reported maternal mortality, demonstrating no difference between  
13 281 groups,<sup>47</sup> and none reported major maternal morbidity (Table 2b).  
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17 282 Three small, crossover RCTs examined the use of selective serotonin receptor inhibitors  
18 283 (SSRIs) compared with placebo (n=55). All studies showed a significant reduction in BP with  
19 284 SSRIs compared to placebo (range 25.6 – 34mmHg).<sup>48-50</sup> These data suggest efficacy for this  
20 285 drug class in hypertension management but do not provide any information regarding relative  
21 286 effectiveness compared to standard antihypertensive drugs. Only one study reported safety  
22 287 data: although no statistical analysis was performed, there were a number of side effects  
23 288 reported in the intervention group.<sup>49</sup>  
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30 289 Two studies evaluated alternative therapies (n=117): there was no difference in BP control  
31 290 with L-arginine supplementation compared with placebo (one RCT, n=45).<sup>51</sup> One reported  
32 291 accelerated recovery of albuminuria with the administration of shengkangbao (Chinese herbal  
33 292 medicine) versus placebo (one quasi-randomised study, n=72). However, the clinical  
34 293 relevance of this outcome is uncertain, there was no difference between groups in the  
35 294 secondary outcomes of systolic BP, diastolic BP or serum creatinine and no safety data were  
36 295 reported.<sup>52</sup>  
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43 296 A single RCT assessed corticosteroids in the management of severe preeclampsia postpartum  
44 297 (n=157).<sup>53 54</sup> No difference was demonstrated between groups in the primary outcome of  
45 298 antihypertensive medication requirement, or in the secondary outcomes of mean arterial  
46 299 pressure (MAP) or need for critical care admission, and no safety data were reported. There  
47 300 were small, statistically significant differences found in some laboratory values (platelet  
48 301 count, lactate dehydrogenase and aspartate transaminase). However, the authors  
49 302 acknowledged that the absolute differences were too small to be clinically relevant.<sup>53</sup>  
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55 303 A very small retrospective cohort study suggested an improvement in MAP with the addition  
56 304 of carperitide (atrial natriuretic peptide) to standard therapy (n=16), and no adverse effects  
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3 305 related to the intervention were reported.<sup>47</sup> However, the magnitude of the difference was not  
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5 306 published, and the study was too small to draw any firm conclusions.

### 7 307 *Uterine curettage*

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9 308 Six RCTs and two prospective cohort studies (n=837) have explored the role of uterine  
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11 309 curettage in postpartum hypertension management. Uterine curettage is a similar process to  
12  
13 310 that used in the surgical management of miscarriage: the lining of the uterus is scraped after  
14  
15 311 completion of the third stage of labour in order to maximise placental tissue removal. This  
16  
17 312 may be under direct vision following caesarean section, or via the transcervical route  
18  
19 313 following vaginal birth. The latter approach may be ultrasound-guided and necessitates some  
20  
21 314 form of anaesthesia. The theory underlying this intervention is that gestational hypertension  
22  
23 315 and preeclampsia are placenta-mediated, and therefore ensuring complete evacuation of the  
24  
25 316 uterus following childbirth may accelerate recovery.<sup>55 56</sup>

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27 317 Seven studies explicitly stated they included both participants who delivered vaginally and  
28  
29 318 those delivered by caesarean: four reported numbers undergoing vaginal delivery (n=248)  
30  
31 319 and caesarean (n=321). One made no comment about the mode of birth.<sup>57</sup> Only one study  
32  
33 320 reported maternal mortality: no difference between groups.<sup>15</sup> Two reported major maternal  
34  
35 321 morbidity, but neither performed any statistical analysis (Table 2b). However, both studies  
36  
37 322 did suggest a reduction in the absolute number of eclamptic seizures in the curettage group  
38  
39 323 compared to no intervention.<sup>15 58</sup> In one, however, there was a relevant difference between the  
40  
41 324 study groups: 28/28 (100%) in the control group were eclamptic at enrolment, compared to  
42  
43 325 9/20 (45%) in the intervention group.<sup>58</sup> Four studies reported safety data, with none reporting  
44  
45 326 any complications related to the intervention (Table 2b).<sup>59-62</sup>

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47 327 All eight studies compared curettage with standard care (i.e. no additional intervention), and  
48  
49 328 all suggested that uterine curettage resulted in a significantly lower BP.<sup>15 18 57-62</sup> One of these  
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51 329 had two control groups: standard care, and oral nifedipine; when compared to oral nifedipine,  
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53 330 no difference was noted with curettage.<sup>60</sup>

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55 331 Five studies reported the magnitude of the difference in MAP between curettage and standard  
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57 332 care: range 6-13mmHg.<sup>15 18 59 60 62</sup> Only two of these reported BP data beyond 24 hours  
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59 333 postpartum: one RCT reported a significantly lower MAP at 48 hours with curettage  
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334 (intervention group 104mmHg, control group 113mmHg, difference 9mmHg,  $p=0.0017$ ;  
335  $n=45$ ),<sup>60</sup> but the other RCT demonstrated no significant difference in MAP at 48 hours  
336 (n=420).<sup>15</sup>

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3 337 One study demonstrated that a greater proportion of the intervention group attained the target  
4 338 BP of <140/90mmHg at 24 (intervention group 9/20 (45%), control group 3/28 (11%):  
5 339 difference 34%, no *p*-value quoted) and 48 hours postpartum (intervention group 14/20  
6 340 (70%), control group 8/28 (29%): difference 41%, no *p*-value quoted).<sup>58</sup> Two studies did not  
7  
8 341 present the size of the difference between groups.<sup>57 61</sup>

## 12 13 342 **Discussion**

14 343 This review found evidence demonstrating that calcium-channel blockers, vasodilators and  
15 344 beta-blockers lower BP postpartum, but no clear answer to which was most effective and  
16 345 should, therefore, be preferentially prescribed. All but two studies examined the acute control  
17 346 of severe hypertension or short term BP control whilst women remained in hospital  
18 347 postpartum,<sup>25 37</sup> and so provide little guidance about prescription in the weeks after discharge.  
19 348 Moreover these both examined thiazide diuretics, not recommended in the UK for use whilst  
20 349 breastfeeding.<sup>8</sup> Complete safety data were limited across trials, as were data regarding  
21 350 objective clinical outcomes and two further studies examined antihypertensive agents not  
22 351 recommended for use postpartum in the UK (methyldopa and reserpine).<sup>63 64</sup> One trial  
23 352 evaluated captopril at a much higher daily dose than the UK recommended daily starting  
24 353 dose.<sup>64</sup>

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34 354 Uterine curettage is not currently recommended, due to safety concerns regarding additional  
35 355 anaesthetic and operative risks, and the availability of alternative treatments to lower BP,  
36 356 particularly in the context of vaginal birth.<sup>65</sup> However, the included studies consistently  
37 357 demonstrated that uterine curettage improved BP control versus standard care,<sup>15 18 57-62</sup> with  
38 358 one reporting an equivalent effect to oral nifedipine.<sup>60</sup> Amongst the limited safety data none  
39 359 reported an excess complication rate (infection or uterine damage) with curettage, but given  
40 360 the low incidence of operative complications, the total population (n=837) was likely  
41 361 insufficient to adequately address potential competing risks. Furthermore, these studies did  
42 362 not demonstrate any impact from curettage on maternal mortality or severe morbidity and  
43 363 concerns exist about some studies' methodology. The evidence reviewed is insufficient to  
44 364 recommend incorporation of this intervention into routine clinical practice.

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53 365 Four trials evaluating loop diuretics failed to provide conclusive evidence of benefit. Three  
54 366 produced non-significant results in their main analysis,<sup>16 19 46</sup> and the single conference  
55 367 abstract which did suggest better BP control with oral furosemide, did not publish the  
56 368 magnitude of the difference, rendering it difficult to assess the clinical relevance.<sup>45</sup> In contrast



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3 369 to the Cochrane review, we conclude that, at present, there is no evidence to support the  
4 370 routine use of diuretics postpartum.<sup>10</sup>  
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7 371 We found no adequate evidence to support alternative medications or a particular care model  
8 372 in the management of HDP postpartum. SSRIs substantially reduced BP versus placebo,<sup>48-50</sup>  
9 373 but no published data was identified comparing their efficacy with standard antihypertensive  
10 374 treatment, making it difficult to draw meaningful conclusions about their clinical application.  
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12 375 Neither study evaluating postpartum care organisation reported maternal mortality or  
13 376 morbidity, or any measure of BP control, with both selecting postnatal readmissions as their  
14 377 primary outcome. An increased postnatal readmission rate, however, may not necessarily  
15 378 reflect harm: it might instead suggest that a particular model of care can better detect  
16 379 problems in the community and admit appropriately, ultimately resulting in a lower risk to  
17 380 patients.  
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24 381 In light of the heterogeneous nature of research in this field, when designing this review, we  
25 382 included all interventions targeting hypertension management, but not end-organ  
26 383 complications, including eclampsia. Therefore, trials evaluating magnesium sulphate were  
27 384 outside the scope of this review. We acknowledge the relevance of this therapy in women  
28 385 with severe pre-eclampsia, especially in the immediate postnatal period, and a Cochrane  
29 386 review suggests there is no uncertainty regarding the effectiveness of this therapy.<sup>66</sup>  
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35 387 A strength of this review is that cohort studies, case-control studies and quasi-randomised  
36 388 studies were eligible in addition to RCTs, and no language or date restrictions were imposed,  
37 389 resulting in a comprehensive review that provides evidence suggesting significant research  
38 390 gaps, consistent with the findings from the Cochrane review (2013).<sup>10</sup> The applicability of the  
39 391 findings and recommendations from this review are restricted by the low quality of included  
40 392 studies: both reviewers judged the vast majority to be at high overall risk of bias. Nearly one-  
41 393 quarter of the included studies were published only as conference abstracts, and therefore not  
42 394 subjected to peer review. Data extraction was restricted to the information provided in the  
43 395 abstracts (no authors provided additional data upon request). These were limiting factors in  
44 396 our analysis, but we nonetheless felt it was important to include these studies for  
45 397 completeness, especially given the paucity of evidence that exists in this field. A further  
46 398 justification for their inclusion is that half of the trials reported in conference abstracts never  
47 399 reach full publication, and positive trials are more likely to be published than negative ones,<sup>67</sup>  
48 400 which has the potential to skew the results of a review if they are omitted.  
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3 401 A further limitation of this review is that the majority of identified studies did not report  
4 402 substantive clinical outcomes such as maternal mortality, morbidity or harms. Without these,  
5 403 it is difficult to define properly the potential role of proposed interventions in clinical  
6 404 practice. The incidence of adverse maternal and neonatal outcomes, particularly in high  
7 405 resource settings, is low meaning adequately powering studies for real outcomes of interest is  
8 406 financially demanding. Therefore researchers often employ surrogate outcomes. Additionally,  
9 407 the range of outcomes reported in included studies was broad and inconsistent, with BP  
10 408 changes in particular being measured in a variety of different ways, further limiting the  
11 409 comparability of trials. Increasingly, core-outcome sets are being produced, with a view to  
12 410 trials reporting as standard, a minimum set of outcomes that are clinically meaningful and  
13 411 important to patients.<sup>68</sup> We hope in future this would enhance our ability to synthesise results  
14 412 from different studies to produce high-quality evidence. There is consensus about trying to  
15 413 move away from surrogate outcomes, for example time to BP control, as they cannot  
16 414 effectively substitute for clinically important outcomes. An important and clinically  
17 415 meaningful end point should measure how a patient feels, functions, or survives.

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29 416 The Cochrane review included only nine randomised trials (author names in bold in  
30 417 Appendix S4). We believe our review adds to this, as an additional 30 studies are included  
31 418 (19 pre-dating the Cochrane search, and 11 subsequent to it), providing a current and  
32 419 complete summary of all available research in the field. The contrast between the scales of  
33 420 the two reviews highlights a lack of high quality evidence, despite a reasonably high number  
34 421 of research studies being conducted to answer the question about how hypertension should be  
35 422 managed postpartum in women with HDP. In future, studies need to be more robust and  
36 423 better designed to address the research questions adequately. Furthermore, in spite of these  
37 424 extensions, the body of evidence identified was substantially smaller than that underpinning  
38 425 antenatal hypertension management: eighteen studies (n=982), not restricted to RCTs,  
39 426 evaluated antihypertensive medications postpartum. Furthermore, the size of all but a few  
40 427 individual studies was small. In comparison, a Cochrane review (2014) evaluating  
41 428 antihypertensive medication for mild to moderate hypertension in pregnancy included 49  
42 429 RCTs (n=4,723).<sup>69</sup> Moreover, the quantity and quality of evidence supporting the  
43 430 management of HDP is vastly less than that available for essential hypertension outside  
44 431 pregnancy, where individual RCTs commonly involve several thousand participants.<sup>70</sup>

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56 432 This review demonstrates a lack of good quality evidence for postpartum hypertension  
57 433 management, emphasising the need for further RCTs directly comparing different

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3 434 antihypertensive agents, BP thresholds for medication adjustment and different models of  
4 435 care, with outcome measures other than postnatal readmissions. We believe the studies  
5 436 examining uterine curettage justify further research to evaluate clinically meaningful  
6 437 outcomes and procedural risks. It might be pragmatic to confine this to curettage at caesarean  
7 438 section, given concerns regarding surgical intervention after vaginal birth: an additional  
8 439 anaesthetic is not required; infection risk is lowered within a sterile surgical field compared to  
9 440 the transcervical route, and curettage under direct vision limits perforation risk. This might be  
10 441 beneficial in women with severe preeclampsia where BP control during pregnancy has been  
11 442 challenging despite multiple medications.<sup>55</sup>  
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## **Details of ethical approval**

No ethical approval was required for this project.

## **Contribution to authorship**

AC drafted the protocol with JD and drafted and piloted the data extraction sheet. These were reviewed by RMcM, LP, KT, LM and PL. NR and AC wrote the search strategy, and the online searches were conducted by NR. AC and LP reviewed the search results independently and carried out the data extraction. This manuscript was drafted by AC and reviewed by RMcM, JD, LP, NR, KT, LM and PL. AC will be the guarantor.

## **Data sharing statement**

The data utilised in this systematic review originate from the research articles cited in this manuscript. These were collected from the published manuscripts. No additional unpublished data are available.

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**Tables and figures**

**Figure 1: PRISMA Flowchart**

See separate document.

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**Table 1: Outcome measures**

	<b>Outcome measures</b>	<b>Timing</b>
<b>Primary outcome(s)</b>	Maternal mortality	Direct maternal deaths up to day 42 postpartum; later maternal deaths up to 1 year postpartum
	Maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure; development of preeclampsia with severe features; postnatal complication requiring intervention)	
	Systolic blood pressure control	
	Diastolic blood pressure control	
	Mean arterial pressure control	
	Safety data (adverse events or maternal side effects)	
<b>Secondary outcome(s)</b>	Critical care admission	
	Length of hospital stay following delivery	
	Postnatal readmission to secondary care	
	Antihypertensive medication requirement	
	Urine output	
	Laboratory values Other as defined by study	

Table 2a: Primary outcome and safety data reporting in included studies (Antihypertensive medications, 18 studies)

Study ID	Intervention	Control	Primary outcome assessment			Safety data reporting	Results (for reported outcomes)	
			Maternal mortality	Maternal morbidity	SBP control			DBP control
<b>CALCIUM CHANNEL BLOCKERS (3 studies)</b>								
Barton 1990 <sup>32</sup>	Nifedipine (oral)	Placebo			●	●	●	SBP control: no significant difference. DBP control: no significant difference. MAP control: improved in intervention group (difference 6.3mmHg, p<0.05).
Vermillion 1999 <sup>21</sup>	Nifedipine (oral)	Labetalol (IV bolus)			●	●	●	SBP control: improved in intervention group (difference in time to target BP 18.5 minutes, p=0.002). DBP control: improved in intervention group (difference in time to target BP 18.5 minutes, p=0.002). Safety: no significant difference. 1/25 intervention group became hypotensive.
Sayin 2005 <sup>34</sup>	Nifedipine (oral)	Methyldopa (oral)	●		●	●		Maternal mortality: no significant difference. SBP control: no significant difference. DBP control: no significant difference.
<b>VASODILATORS (6 studies)</b>								
Palot 1979 <sup>36</sup>	Hydralazine (IV infusion) plus furosemide (IV bolus)	Clonidine (IV) plus furosemide (IV bolus)		●				Maternal morbidity: no statistical analysis.
Griffis 1989 <sup>38, 39</sup>	Hydralazine (IM)	Methyldopa (IV bolus)				●	●	MAP control: no significant difference. Safety: no significant difference. No side effects reported in either group.
Walss Rodriguez 1991 <sup>40</sup>	Hydralazine (oral) plus nifedipine (oral, as required)	Nifedipine (oral, as required)			●	●		SBP control: no significant difference. DBP control: no significant difference.
Begum 2002 <sup>17</sup>	Hydralazine (IV bolus)	Hydralazine (IV infusion)				●	●	DBP control: improved in intervention group (difference in time to target DBP 121.1 minutes, p<0.001). Safety: no significant difference. No side effects reported in either group.
Vigil de Gracia 2007 <sup>35</sup>	Hydralazine (IV bolus)	Labetalol (IV bolus)	●	●	●	●	●	Maternal mortality: no significant difference. Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. Small numbers of side effects reported in both groups.
Hennessy 2007 <sup>23</sup>	Diazoxide (IV bolus)	Hydralazine (IV bolus)			●	●		SBP control: improved in intervention group (difference in percentage achieving target BP 23%, p<0.01). DBP control: improved in intervention group (difference in percentage achieving target BP 23%, p<0.01).
<b>BETA BLOCKERS (5 studies)</b>								
Garden 1982 <sup>24</sup>	Labetalol (IV infusion)	Dihydralazine (IV infusion)				●	●	DBP control: no statistical analysis. Safety: no statistical analysis. 1/6 intervention group developed bronchospasm. 4/6 control group developed tachycardia and 1/6 developed oliguria. 4/6 control group – drug stopped due to a precipitous fall of DBP to 40-50mmHg.

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
Fidler 1982 <sup>42</sup>	Timolol (oral)	Methyldopa (oral)			●	●	●	SBP control: improved in intervention group (difference 5.1mmHg, p<0.05). DBP control: no significant difference. Safety: no statistical analysis. 1/40 intervention group became disorientated. 1/40 control group became hypotensive and 1/40 became drowsy.	
Mabie 1987 <sup>22</sup>	Labetalol (IV bolus)	Hydralazine (IV bolus)					●	MAP control: improved in control group (difference 7.8mmHg (p 0.02)). Safety: no statistical analysis. 1/40 intervention group developed scalp tingling. 2/20 control group developed headaches.	
Shumard 2016 <sup>41</sup>	Labetalol (oral)	Nifedipine (oral)			●	●		SBP control: improved in control group (difference in time to achieve target BP 1 day, p=0.0031). DBP control: improved in control group (difference in time to achieve target BP 1 day, p=0.0031).	
Sharma 2017 <sup>27 28</sup>	Labetalol (oral)	Nifedipine (oral)			●	●	●	SBP: no significant difference. DBP: no significant difference. Safety: No major side effects reported in either group. Minor side effects more commonly reported in control group (20% intervention, 48% control, p=0.04).	
<b>THIAZIDES (2 studies)</b>									
Gaisin 2013 <sup>25</sup>	Indapamide (oral)	Methyldopa (oral)			●	●	●	SBP control: no significant difference. DBP control: no significant difference. Safety: no statistical analysis, no details reported.	
Gaisin 2014 <sup>37</sup>	Indapamide (oral) plus ursodeoxycholic acid (oral)	Methyldopa (oral)			●	●	●	SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.	
<b>INDOLE ALKALOIDS (1 study)</b>									
Krebs 1956 <sup>43 44</sup>	Reserpine (oral or IM)	Phenobarbital			●	●	●	SBP control: no statistical analysis. DBP control: no statistical analysis. Safety: no statistical analysis. No adverse events reported in intervention group, no comment on control.	
<b>CENTRALLY-ACTING ALPHA-AGONISTS (1 study)</b>									
Noronha Neto 2016 <sup>29-31</sup>	Clonidine (oral)	Captopril (oral)	●	●	●	●	●	Maternal mortality: no significant difference. Maternal morbidity: no significant difference. SBP control: improved in intervention group (difference in number of episodes of high BP (1.4, p<0.08)). DBP: improved in intervention group (difference in number of episodes of high BP (1.4, p<0.08)). Safety: no significant difference. Adverse reactions 18.6% intervention, 28.8% control, p=NS.	

**Table 2b: Primary outcome and safety data reporting in included studies (Loop diuretics, other drugs, uterine curettage and organisation of care, 21 studies)**

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
<b>LOOP DIURETICS (4 studies)</b>									
Matthews 1997 <sup>46</sup>	Furosemide (oral)	Placebo					●	MAP control: no significant difference.	
Ascarelli 2005 <sup>16</sup>	Furosemide (oral)	No intervention		●	●	●		Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference.	
Amorim 2015 <sup>45</sup>	Furosemide (oral)	Placebo			●	●	●	SBP control: improved in intervention group (difference not stated, p<0.001). DBP control: improved in intervention group (difference not stated, p<0.001). MAP control: improved in intervention group (difference not stated, p<0.001).	
Veena 2017 <sup>19</sup>	Furosemide (oral) + nifedipine (oral)	Nifedipine (oral)		●	●	●	●	Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference.	
<b>OTHER DRUGS (7 studies)</b>									
<b>Selective 5-HT antagonists</b>									
Weiner 1982 <sup>48</sup>	R41468 (intravenous infusion)	Placebo					●	MAP control: improved in intervention group (difference 25.6mmHg, p<0.001). SBP control: improved in intervention group (difference in SBP decline 34mmHg, p<0.001). DBP control: improved in intervention group (difference in DBP decline 27mmHg, p<0.001).	
Weiner 1984 <sup>49</sup>	Ketanserin (IV infusion)	Placebo		●	●	●	●	MAP control: improved in intervention group (difference not stated, p<0.001) Safety: No statistical analysis. 3/20 intervention group experienced blurred vision: 1 of these was hypotensive (responded to hydration). 1/20 intervention group experienced mild euphoria.	
Montenegro 1985 <sup>50</sup>	Ketanserin (IV bolus +/- infusion)	Placebo		●	●	●	●	SBP control: improved in intervention group (absolute difference not stated, p<0.001). DBP control: improved in intervention group (absolute difference not stated, p<0.001). MAP control: improved in intervention group (absolute difference not stated, p<0.001).	
<b>Alternative therapies</b>									
Hladunewich 2006 <sup>51</sup>	L-arginine (oral or IV bolus)	Placebo			●	●	●	SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.	
Liu 2009 <sup>52</sup>	Shengkangbao (oral or IV bolus)	No intervention			●	●		SBP control: no significant difference. DBP control: no significant difference.	



Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control		
<b>Steroids</b>									
Barrilleaux 2005 <sup>53 54</sup>	Dexamethasone (IV bolus)	Placebo					●	MAP control: no significant difference.	
<b>Atrial natriuretic peptide</b>									
Shigemitsu 2015 <sup>47</sup>	Carperitide (route not specified)	No intervention	●				●	Maternal mortality: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.	
<b>UTERINE CURETTAGE (8 studies)</b>									
Salvatore 1967 <sup>58</sup>	Uterine curettage	No intervention		●	●	●		Maternal morbidity: no statistical analysis. SBP control: no statistical analysis. DBP control: no statistical analysis.	
Magann 1993 <sup>59</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at different time points to 24h postpartum 6-10mmHg, p<0.05). Safety: no significant difference. No complications reported from intervention (follow-up to 7 weeks postpartum).	
Magann 1994 <sup>60</sup>	Uterine curettage	Nifedipine (oral) or no intervention					●	MAP control: no significant difference between intervention and oral nifedipine; improved in intervention group compared to no intervention (difference at 8-48h postpartum 9-13mmHg, p=0.0017). Safety: no significant difference. No complications/side effects reported from interventions (follow-up to 7 weeks postpartum).	
Gocmen 1996 <sup>57</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, p=0.01).	
Gomez 2005 <sup>61</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, p<0.001). Safety: no significant difference. No complications reported from intervention.	
Alkan 2006 <sup>62</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference 6.8mmHg, p<0.05). Safety: No significant difference. No complications reported from intervention.	
Ragab 2013 <sup>15</sup>	Uterine curettage	No intervention	●	●			●	Maternal mortality: no significant difference. Maternal morbidity: no statistical analysis. MAP control: improved in intervention group (difference at 6h postpartum 12.3mmHg, P=0.02, difference at 24h postpartum 9.2mmHg, p=0.01)	
Mallapur 2015 <sup>18</sup>	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at 4h postpartum 7.6mmHg, p<0.001).	
<b>ORGANISATION OF CARE (2 studies)</b>									
York 1997 <sup>26</sup>	Nurse specialist follow-up	No intervention						N/A	
Bibbo 2014 <sup>33</sup>	Specialist postpartum clinic	No intervention						N/A	

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**Legend for Tables 2a&b**

● = improved in intervention group; ● = no significant difference; ● = improved in control group; ● = unclear

For primary outcome assessment where there was a significant difference between groups, the magnitude of the difference is reported; where any adverse events or side effects were reported this is presented

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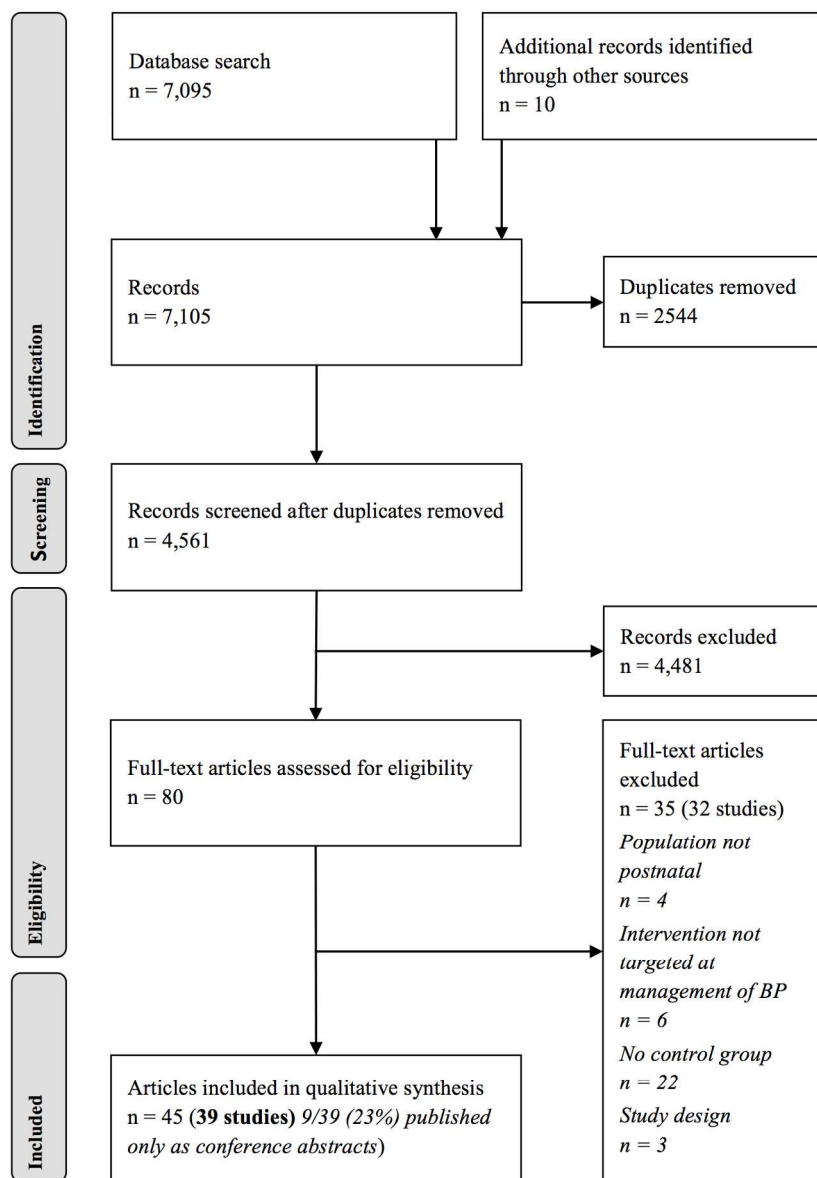


Figure 1: PRISMA Flowchart

137x193mm (300 x 300 DPI)



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**Appendix S1: Management of hypertensive disorders of pregnancy in the postpartum period: A systematic review protocol**

**Registration:** PROSPERO CRD42015015527

[http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015015527#.VL4ZI9KsWCK](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527#.VL4ZI9KsWCK)

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**Amendments:** Protocol first published 22/12/2014 (version 1.0). Protocol amended (version 2.0 25/03/2015) to include all reporting items from the PRISMA-P 2015 checklist, and PROSPERO registration number.

**Review funder:** NIHR Collaborations for Leadership in Applied Health Research and Care (funding A Cairns' fellowship)

**Review sponsor:** University of Oxford

**Abstract**

**Rationale:** Hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia) are a leading cause of direct maternal death in the UK, and affect approximately 5-10% of pregnancies. Hypertensive disorders of pregnancy persist during the postpartum period, and complications can occur during this time.

**Research question:** How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

**Objectives:**

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

**Search strategy:** Medline and nine other electronic databases will be searched for articles published from inception until October 2014 using a search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period.

**Study eligibility criteria:**

*Population:* postnatal women with gestational hypertension or pre-eclampsia as defined by study

*Intervention:* therapeutic intervention for hypertensive disorders of pregnancy

*Comparisons:* another intervention, placebo or no intervention

*Study design:* RCT, prospective or retrospective cohort study or case-control study

*Publication date:* no restrictions

*Language:* no restrictions

**Data management and extraction:** Two reviewers will first review the titles of articles yielded by the search, and then the abstracts of articles of potential relevance. The full papers of potentially eligible papers will be assessed, and data extracted independently by the two reviewers using a data extraction sheet. Differences in study selection and data extraction will be resolved by discussion.

**Assessment of methodological quality:** This will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, and for the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales.

**Systematic review registration:** This systematic review is registered with PROSPERO (International prospective register of systematic reviews).



## Rationale

### *Definitions*

The National Institute for Health and Clinical Excellence (NICE) defines gestational hypertension as new-onset raised blood pressure ( $\geq 140/90$ mmHg) beyond 20 weeks gestation. NICE defines pre-eclampsia as new-onset raised blood pressure ( $\geq 140/90$ mmHg) together with new-onset significant proteinuria ( $\geq 300$ mg/24hr), beyond 20 weeks gestation (1).

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as new-onset raised blood pressure (as defined by NICE) in association with one of new-onset significant proteinuria (as defined by NICE), maternal organ dysfunction or uteroplacental insufficiency (2).

### *Epidemiology*

Hypertensive disorders of pregnancy remain the second commonest direct cause of maternal death in the USA (3). Until recently this has also been the case in the UK (CMACE 2006-8)(4), but the most recent Confidential Enquiry into maternal deaths showed that for the triennium 2009-11, pre-eclampsia and eclampsia was the fourth commonest cause of direct death (behind thrombosis, genital tract sepsis and haemorrhage), with a rate of 0.42 deaths per 100,000 maternities (5).

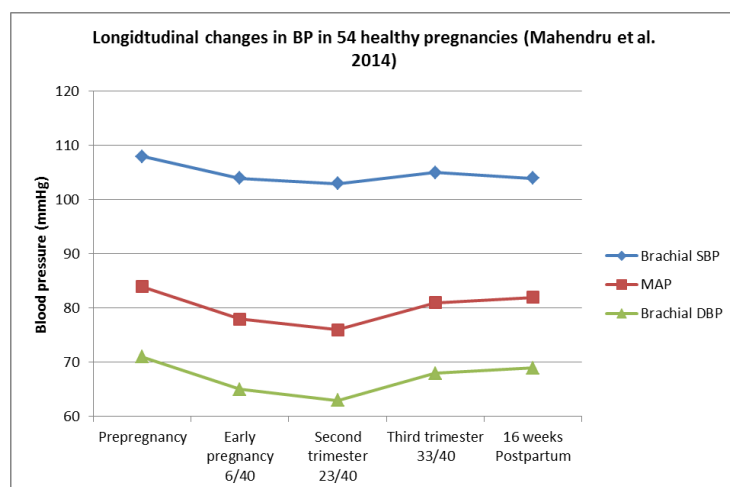
A recent population-based retrospective study in the United States found the rate of pre-eclampsia to be 3.4%. This study showed a slight, but significant increase, in the rates of both mild, and to a greater extent, severe pre-eclampsia over the period studied (1980-2010) (6).

Reviews of the literature, and national guidelines, quote rates of gestational hypertension between 6% (7) and 15% (8). A retrospective study using data from the National Hospital Discharge Survey in the United States (1987-2004) demonstrated an incidence of 30.6 cases of gestational hypertension per 1000 deliveries in 2003-2004 (3.1%) (9). In a well-designed large randomised controlled trial assessing preventative strategies for hypertensive disorders of pregnancy in low risk, nulliparous women the incidence of gestational hypertension across both groups was 6% (10).

### *Physiology of blood pressure in pregnancy and postpartum*

As a result of a significant decrease in systemic vascular resistance (as early as 5 weeks gestation) (11) there is a decrease in arterial pressures from early in the first trimester. Arterial pressures reach a nadir in the second trimester, and then begin to rise in the third trimester, before reaching near-preconception levels in the postnatal period (12).

**Figure 1: Serial blood pressures before, during and after pregnancy (reproduced from the data of Mahendru et al. 2014) (12)**



In gestational hypertension and pre-eclampsia the normal pregnancy-induced vasodilatation is reversed. In untreated women with pre-eclampsia significant increases in systemic vascular resistance are seen and result in elevation of blood pressure (13).

### ***Hypertensive disorders of pregnancy in the postpartum period***

There has been considerable focus on blood pressure control during pregnancy, especially with respect to pregnancy outcome. However, it is recognised that hypertensive disorders of pregnancy do persist during the postpartum period, and that complications can occur during this time. A small retrospective observational study published in 1987 looked at 67 women with moderate-severe pre-eclampsia: there was often an initial decrease in blood pressure after delivery, but this was followed by a rise to hypertensive levels in many women. In 50% of cases the blood pressure was 150/100mmHg or higher on day 5 after birth. The authors recommended continuing blood pressure monitoring and treatment in the postpartum period for women with a diagnosis of pre-eclampsia (14).

Most women with hypertensive disorders of pregnancy will be treatment-free by 3 months postpartum. In women whose blood pressure normalised after delivery the mean time to normalisation in a retrospective cohort study of 62 women was 5.4 weeks (15). This rapidly changing blood pressure, with shifting medication requirement, poses an additional challenge in terms of how best to manage this down-titration.

Approximately one third of eclamptic seizures occur postpartum, and studies suggest that over half of these seizures occur more than 48 hours after birth. Chames et al. (2002) highlight the importance of education of women and clinicians regarding prodromal symptoms of eclampsia in the postnatal



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period (16). A case series published in 2005 of patients who sustained a stroke in association with severe pre-eclampsia or eclampsia, showed that more than half (57%) of these strokes occurred in the postpartum period (17).

### **Current guidelines**

NICE guidelines highlight that very few clinical studies have addressed the management of blood pressure postpartum, and in practice clinical care is typically to continue antepartum antihypertensive medication and monitor blood pressure in the community with a focus on prevention of over-treatment.

NICE recommend frequency of monitoring in the postnatal period for both pre-eclampsia and gestational hypertension. The guidelines also stipulate thresholds for considering increasing or starting anti-hypertensive medication during this period (150/100 mmHg), and for reduction or stopping anti-hypertensive medication (consider at < 140/90 mmHg, and reduce at < 130/80 mmHg) (1).

### **Research question**

How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

### **Objectives**

The aim is to establish what evidence exists to guide the optimal approach to management of gestational hypertension and pre-eclampsia in the postnatal period. We want to address the specific sub-questions:

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

### **Information sources and search strategy**

The systematic review of 'management of hypertensive disorders of pregnancy in the postpartum period' will be conducted in line with the PRISMA statement (18). Completion of a systematic review





is an iterative process, and it may be that modifications to the original review protocol are required during its conduct.

A search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period will be developed by an experienced trial search co-ordinator. Potentially relevant studies will be identified following screening of title and abstract of studies captured by the search and full text assessed for suitability.

Resources to be searched from inception to October 2014:

- Medline (Appendix 3) and 9 other electronic databases
- Trial registers (ClinicalTrials.gov; Current Controlled Trials; WHO; PROSPERO)
- Meta Search Engines
- Hand searches of reference lists
- Citation searching on Scopus and Web of Science
- Related articles search on PubMed
- Contact with authors and professional bodies / organisations: Experts in this field will be contacted for their recommendations of potentially relevant citations (19)

## Study eligibility criteria

### **INCLUSION CRITERIA**

**Population:** postnatal women with hypertensive disorders of pregnancy (gestational hypertension or pre-eclampsia).

**Intervention:** therapeutic intervention for management of hypertensive disorders of pregnancy

**Comparisons:** other intervention, placebo or no intervention

**Study design:** randomised controlled trial, cohort study (prospective and retrospective) or case-control study; human studies only

**Publication Date:** no restrictions

**Language:** no restrictions

### **EXCLUSION CRITERIA**

Exclude report / study if **any** exclusion criteria fulfilled:

**Population:** antenatal or intrapartum women with hypertensive disorders of pregnancy; end-organ complications of pre-eclampsia (eclampsia, renal failure, HELLP syndrome)



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**Intervention:** treatment of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets); prevention or management of eclampsia; prevention of postpartum hypertension; choice of anaesthetic or sedative in pre-eclampsia; observational studies

**Comparisons:** no control group

**Study design:** guidelines, reviews, expert opinions, letters, commentaries, audits, case series and case reports excluded; animal studies

### Data extraction

Two reviewers (AC and LP) will screen the titles and abstracts of articles yielded by the search against the eligibility criteria. Discrepancies will be resolved by consensus before determining the list of full papers for review. The reports will be screened independently by the two reviewers, and discrepancies will be resolved by discussion before deciding which papers to include in the review.

Data from included studies will be extracted independently by the two reviewers using a piloted and standardised data extraction sheet. Differences in data extraction will be resolved by discussion.

In the event that there is more than one report published about a single study: the reports will be reviewed separately but the data from that study grouped in our analysis, and the primary reference will be used.

In the event that data is missing from a report (for example the sole publication is a conference abstract) we will contact the authors directly to request further detail.

The study characteristics (study size, population, setting, study design, methodology, intervention, controls if applicable, outcome measures, and follow up period) will be recorded and reported.

### Data synthesis

The data extracted will be aggregate.

Due to the heterogeneous nature of the outcomes reported in these studies a narrative synthesis is planned.

For trials where the population study is peripartum (i.e. a mixture of antepartum, intrapartum and postpartum) we will extract the data for the postpartum women and analyse this. If this is not feasible from the reported data then we will contact the study authors to request the data for this subgroup.

### Outcomes

The results of all clinically relevant outcomes in hypertensive disorders of pregnancy that would be important to clinicians and patients will be extracted and reported.

The main outcomes we are interested in are listed in table 1 below:



Table 1

	Outcome measures	Timing
<b>Primary outcome(s)</b>	Maternal mortality Major maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure) Systolic blood pressure control Diastolic blood pressure control Mean arterial pressure control	Direct maternal deaths upto day 42 postpartum; later maternal deaths upto 1 year postpartum
<b>Secondary outcome(s)</b>	Critical care admission Postnatal readmission to secondary care Length of hospital stay following delivery Anti-hypertensive medication requirement Maternal side effects of intervention Development of pre-eclampsia with severe features Postnatal complication requiring intervention Urine output Laboratory values	

### Assessment of methodological quality

We will assess the risk of bias in each study. For randomised trials this will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Appendix 1, Table 2) (20). For each study the key domains will be identified, and then an overall assessment of bias within each trial made, according to the guidance published by the Cochrane Collaboration (Appendix 1, Table 2).

For the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales (Appendix 2, Tables 4 and 5) (21).

We will make a global assessment of bias across trials, based on the guidance from the Cochrane Collaboration (Appendix 1, Table 3):

- EITHER Most information is from trials at low risk of bias;
- OR most information is from trials at low or unclear risk of bias;
- OR the proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

**Discussion**

A Cochrane Review (2013) addresses the question of 'prevention and treatment of postpartum hypertension'. This only includes randomised controlled trials (9 in total), and does not address the issue of monitoring blood pressure during this period (22). Given the paucity of evidence cited in this area we believe there is a place for a review looking at all available evidence for the optimal approach to management of hypertensive disorders of pregnancy in the postpartum period.

**Conflicts of interest**

Neither AC nor LP have any conflicts of interest.

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## Appendix 1

**Table 2:** Cochrane Collaboration's tool for assessing risk of bias (*adapted from Higgins and Altman*)(20)

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
<b>Selection bias</b>	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
<b>Performance bias</b>	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
<b>Detection bias</b>	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
<b>Attrition bias</b>	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
<b>Reporting bias</b>	Selective reporting	State how selective outcome reporting was examined and what	Reporting bias due to selective



		was found	outcome reporting
<b>Other bias</b>	Anything else, ideally Pre-specified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

\*Assessments should be made for each main outcome or class of outcomes.

**Table 3:** Approach to formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials (*adapted from Higgins and Altman*)(20)

Risk of bias	Interpretation	Within a trial	Across trials
<b>Low risk of bias</b>	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
<b>Unclear risk of bias</b>	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
<b>High risk of bias</b>	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results





## Appendix 2

**Table 4: Newcastle-Ottawa quality assessment scale case control studies(21)**

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

<b>Selection</b>	Is the case definition adequate?	a) Yes, with independent validation ✱ b) Yes, e.g. record linkage or based on self-reports c) No description
	Representativeness of the cases	a) Consecutive or obviously representative series of cases ✱ b) Potential for selection biases not stated
	Selection of controls	a) Community controls ✱ b) Hospital controls c) No description
	Definition of controls	a) No history of disease (endpoint) ✱ b) No description of source
<b>Comparability</b>	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the post important factor) ✱ b) Study controls for any additional factor ✱
<b>Exposure</b>	Ascertainment of exposure	a) Secure records (e.g. surgical records) ✱ b) Structured interview where blind to case/control status ✱ c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description
	Same method of ascertainment for cases and controls	a) Yes ✱ b) No
	Non-response rate	a) Same rate for both groups ✱ b) Non-respondents described c) Rate different and no designation

**Table 5: Newcastle-Ottawa quality assessment scale cohort studies(21)**

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

<b>Selection</b>	Representativeness of the exposed cohort	a) Truly representative of the average <<_>> (describe) in the community ✱ b) Somewhat representative of the average <<_>> (describe) in the community ☐ c) Selected group of users e.g. nurses, volunteers d) No description of the derivation of the cohort
	Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort ✱ b) Drawn from a different source c) No description of the derivation of the non-exposed cohort
	Ascertainment of exposure	a) Secure record (e.g. surgical records) ✱ b) Structured interview ✱ c) Written self-report d) No description



	Demonstration that the outcome of interest was not present at start of study	a) Yes * b) No
<b>Comparability</b>	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the post important factor) * b) Study controls for any additional factor *
<b>Outcome</b>	Assessment of outcome	a) Independent blind assessment * b) Record linkage * c) Self-report d) No description
	Was follow-up long enough for outcomes to occur	a) Yes (select an adequate follow up period for outcome of interest) * b) No
	Adequacy of follow-up of cohorts	a) Complete follow-up – all subjects accounted for * b) Subjects lost to follow-up unlikely to introduce bias: >_ _ % (select an adequate %) follow-up rate, or description provided of those lost) * c) Follow-up rate < _ _ % (select an adequate %) and no description of those lost d) No statement



### Appendix 3: Medline search strategy

# ▼	Searches	Results
1	Pregnancy/ and Hypertension/	9226
2	exp Hypertension, Pregnancy-Induced/	29022
3	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or ante-natal or antepart* or ante-part* or obstetric*) and (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti.	6787
4	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or ante-natal or antepart* or ante-part* or obstetric*) adj3 (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti,ab.	12434
5	(eclamp* or preeclamp* or pre-eclamp* or hellp).ti,ab.	25194
6	1 or 2 or 3 or 4 or 5	46611
7	Postnatal Care/	4044
8	Aftercare/	6684
9	Postpartum Period/ and Maternal Health Services/	126
10	exp Puerperal Disorders/ and Maternal Health Services/	196
11	Postpartum period/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	187
12	exp Puerperal disorders/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	237
13	Postpartum period/ and exp Curettage/	30
14	exp Puerperal disorders/ and exp Curettage/	118
15	Postpartum period/ and hypertension/dt, th	33
16	exp Puerperal disorders/ and hypertension/dt, th	54
17	exp Puerperal disorders/dt, th	6408
18	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (care or healthcare or service* or program* or scheme* or intervention*)).ti,ab.	4407
19	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (clinic? or unit? or visit* or referral? or appointment?)).ti,ab.	1491
20	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (manage* or treat* or therap* or medication? or recovery)).ti,ab.	7287
21	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (antihypertens* or anti-hypertens* or calcium channel block* or beta block* or b block* or ace inhibitor* or angiotensin converting enzyme inhibitor* or diuretic*)).ti,ab.	41
22	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (evaluat* or assess* or screen* or diagnos* or monitor* or follow up or supervis*)).ti,ab.	7562
23	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 curet*).ti,ab.	82
24	(postnatal or post-natal or postpart* or post-part* or puerper*).ti.	41491
25	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	64775



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5	26	6 and 25	1896
6	27	((postnatal or post-natal or postpart* or post-part* or puerper*) and (hypertens* or blood pressure)).ti.	270
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9	28	26 or 27	1990
10	29	exp animals/ not humans.sh.	4079856
11	30	(rat or rats or rodent? or mice or mouse or cow or cows or cattle or calf or calves or ewe? or sheep or goat or ruminant? or pig or pigs or minipig? or chicken? or horse or horses or murine or bovine or ovine or porcine or animal?).ti.	1682619
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16	31	29 or 30	4373527
17	32	28 not 31	1881
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For peer review only

**Appendix S2: PRISMA 2009 Checklist**1  
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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7; Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7 (narrative)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	N/A



## Appendix S2: PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7; Appendix S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8; Appendix S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13; Tables 2a+b; Appendix S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8; Appendix S6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

**Appendix S3: Primary reasons for article exclusion (n = 35)**

	Population not postnatal	Intervention not targeted at management of BP	No control group	Study design
<b>n</b>	4	6	22	3
<b>Study IDs</b>	Berks 2015 Gerard 1983 Scardo 1999 Wacker 2006	Chandrasekaran 2015 Ehrenberg 2004 Ehrenberg 2006 Ossada 2016 Wasden 2012 Younger-Lewis 2016	Al Waili 2004 Alicino 1962 Barton 1991 Belfort 1988 Belfort 1992 Bittle 2014 Bosio 2003 Correa 1982 Dulitzky 1987 Hirshberg 2016 Hirshberg 2017 Hunter 1961 Onishi 2015 Robinson 1964 Rodriguez 2012 Saghir Smith 2005 Sukerman-Voldman 1985 Taslimi 1991 Tkacheva 2006 Wacker 1994 Walters 1984	Editor, Emergency Medicine 1990 Cursino 2015 Gallegos 1961

## APPENDIX S4: Main characteristics of included studies (n=39)

Author and year	Methods		Participants				Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary	
<b>ANTIHYPERTENSIVE MEDICATIONS (18 studies)</b>											
<b>Calcium channel blockers</b>											
Barton 1990 <sup>32</sup>	RCT	Enrolled immediately after birth F/U 48h	31	24.0 26.3	Tertiary referral hospital	USA	Nifedipine 10mg PO 4-hourly for 48 hours	Placebo	MAP	SBP, DBP Maternal heart rate AHT requirement Urine output Laboratory values (urine protein, creatinine clearance, HCT, plt, ALT, BUN, creatinine, serum electrolytes, UA, urine specific gravity)	
Vermillion 1999 <sup>21</sup>	RCT	Enrolled within 24h of birth F/U 3 – 24h	21	27.2±7.3 27.0±6.4	Tertiary referral hospital	USA	Nifedipine 10mg stat PO then 20mg every 20min until BP <160/110mmHg or max 5 doses + IV placebo	Labetalol 20mg, then 40mg, then 80mg IV every 20min until BP <160/110mmHg or max 5 doses (300mg) + PO placebo	SBP + DBP	SBP (failure to achieve target <160mmHg) DBP (failure to achieve target <110mmHg) Maternal side effects AHT requirement Urine output	
Sayin 2005 <sup>34</sup>	RCT	Enrolled 24h after birth F/U 72h after BP controlled	83	17-41	Tertiary referral hospital	Turkey‡	Nifedipine 10mg PO QDS until BP <150/100mmHg for 48h	Methyldopa 250mg PO TDS	SBP + DBP	Maternal mortality AHT requirement Hypertensive retinopathy	
<b>Vasodilators</b>											
Palot 1979 <sup>36</sup>	Retrospective cohort study	Not specified	54	24.5 (17-37)	Not specified	France‡	Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose	(1) Clonidine IV and furosemide 20mg IV stat Or (2) Non-systematic treatment	Maternal morbidity (development of pre-eclampsia with severe features)	BP (time to resolution of hypertension)	

**Abbreviations:** AHT = antihypertensive; ALT = alanine aminotransferase; BD = twice daily; BP = blood pressure; BUN = blood urea nitrogen; DBP = diastolic blood pressure; F/U = follow-up; IM = intramuscular; IV = intravenous; MAP = mean arterial pressure; plt = platelets; PN = postnatal; OD = once daily; PO = oral; QDS = four times daily; RCT = randomised controlled trial; SBP = systolic blood pressure; S/L = sublingual; TDS = three times daily; UA = uric acid

\* n = postnatal population (antenatal excluded)

† Where separate data available for study groups, intervention group listed first

‡ Non-English language manuscript



Author and year	Methods		Participants				Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary	
Griffis 1989 <sup>38</sup> 39	RCT	F/U 24h	26	Not specified	Tertiary referral hospital	USA	Hydralazine 20mg IM QDS for 24h	Methyldopa 250mg IV QDS x 24h	MAP	Maternal side effects AHT requirement Urine output (time to diuresis)	
Walss Rodriguez 1991 <sup>40</sup>	RCT	Not specified	38	16-40	Not specified	Mexico†	Hydralazine 40mg PO QDS, duration not specified; if DBP >110mmHg PRN nifedipine 10mg SL every 30min, to max 3 doses	Nifedipine 10mg SL every 30min if DBP ≥110mmHg	SBP	DBP AHT requirement	
Begum 2002 <sup>17</sup>	Quasi-randomised trial	Not specified	15	24.09±4.93 22.72±5.08	Tertiary referral hospital	Bangladesh	Hydralazine 5mg then 2mg IV bolus every 15min until DBP 90-95mmHg	Hydralazine 20mg/200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15min intervals; until DBP 90-95mmHg	DBP	Maternal side effects AHT requirement Maternal heart rate	
Vigil-De Gracia 2007 <sup>35</sup>	RCT	Enrolled day 2-3 after birth F/U not specified	82	29.9±5.9 31.3±5.5	Tertiary referral hospital	Panama	Hydralazine 5mg IV every 20min until BP <160/110mmHg or max 5 doses	Labetalol 20mg, then 40mg, then 80mg IV every 20min until BP <160/110mmHg or max 5 doses (300mg)	SBP + DBP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) Maternal side effects AHT requirement Maternal heart rate	
Hennessy 2007 <sup>23</sup>	RCT	F/U 3h	37	21-43 (mean 33)	Tertiary referral hospital	Australia	Diazoxide 15mg IV every min, maximum dose 300mg	Hydralazine 5mg IV every 2min, maximum 15mg	SBP + DBP	SBP (10mmHg above target after 1 hour) DBP (10mmHg above target after 1 hour) Maternal side effects (including hypotension) Time taken to administer drug	
<b>Beta blockers</b>											
Garden 1982 <sup>24</sup>	RCT	Enrolled immediately after birth F/U 45-64h	6	25-44 20-28	Tertiary referral hospital	South Africa	Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30min until DBP <100mmHg or maximum dose 160mg/h	Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30min until DBP <100mmHg or maximum dose 80mg/h	DBP	Maternal side effects	
Fidler 1982 <sup>42</sup>	RCT	Enrolled 4 days after birth F/U 9 days	80	29.7±1.0 27.8±0.9	Tertiary referral hospital	UK	Timolol 5mg PO TDS for 9 days	Methyldopa 250mg PO TDS for 9 days	DBP	SBP DBP (time to achieve control, proportion achieving control) Maternal side effects	

Author and year	Methods		Participants				Intervention		Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary
Mabie 1987 <sup>22</sup>	RCT	Enrolled 1-96 hours after birth F/U 3h	41	23.7±6.9 22.9±7.0	Tertiary referral hospital	USA	Labetalol 20mg IV every 10min then escalating until DBP <100mmHg or maximum cumulative dose reached (300mg)	Hydralazine 5mg IV every 10min until DBP <100mmHg	MAP	MAP (time to maximal decrease) DBP (achieving target <100mmHg) Maternal side effects AHT requirement Maternal heart rate
Shumard 2016 <sup>41</sup>	Retrospective cohort study	F/U not specified (but >24h)	128	Not specified	Not specified	USA	Labetalol PO (variable dose and frequency)	Nifedipine PO (variable dose and frequency)	Length of hospital stay after birth	SBP, DBP AHT requirement
Sharma 2017 <sup>27, 28</sup>	RCT	F/U not specified (but >24h)	50	Not specified	Tertiary referral hospital	USA	Labetalol 200mg PO BD	Nifedipine XL 30mg PO OD	SBP + DBP	Maternal side-effects Length of PN hospital stay AHT requirement
<b>Other</b>										
Gaisin 2013 <sup>25</sup>	RCT	6 months	30	23-29	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD, duration unclear	Adjusted dose methyldopa	SBP + DBP	Safety data Laboratory values (lipid and glucose metabolism) Adherence to treatment Weight reduction Decrease in albuminuria Decrease in LV mass index Endothelial function Milk production
Gaisin 2014 <sup>37</sup>	RCT	1 year	30	24-28	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD with ursodeoxycholic acid 250mg PO TDS, duration unclear	Adjusted dose methyldopa	SBP + DBP	Maternal side effects Laboratory values (atherogenic lipid profile, glucose metabolism, renal function) Offspring adverse events Weight reduction Decrease in microalbuminuria Decrease in LV mass index Endothelial function
Krebs 1956 <sup>43,44</sup>	Retrospective cohort study	F/U not specified (but >24h)	140	Not specified	Not specified	Switzerland†	Reserpine 0.25mg PO or IM TDS or QDS for 7 days	Phenobarbital	SBP + DBP	SBP + DBP (non-responders) Maternal side effects Resolution of albuminuria Resolution of oedema
Katz 2015 <sup>29,31</sup>	RCT	F/U not specified	90	Not specified	Tertiary referral hospital	Brazil	Clonidine 0.1mg PO repeated every 20min to maximum 6 doses	Captopril 25mg PO repeated every 20min to maximum 6 doses	SBP + DBP	SBP (% reduction) SBP + DBP (daily mean) Maternal side effects AHT requirement
<b>LOOP DIURETICS (3 studies)</b>										
Matthews 1997 <sup>46</sup>	RCT	Enrolled 12-24h after birth F/U 6 weeks	19	Not specified	Tertiary referral hospital	UK	Furosemide 40mg PO OD for 7 days	Placebo	MAP	Length of PN hospital stay AHT requirement Urine output Laboratory values (hypokalemia)

Author and year	Methods		Participants				Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary	
Ascarelli 2005 <sup>16</sup>	RCT	Enrolled 2-24h after birth F/U 6 weeks	264	22.8±6.1 22.9±6.0	Tertiary referral hospital	USA	Furosemide 20mg PO OD + potassium 20mEq PO OD for 5 days	No intervention	SBP	Maternal morbidity (postnatal complication requiring intervention) DBP Length of PN hospital stay AHT requirement Maternal weight Maternal HR Duration of magnesium sulphate	
Amorim 2015 <sup>45</sup>	RCT	Enrolled immediately after birth F/U 5 days	120	Not specified	Tertiary referral hospital	Brazil	Furosemide 40mg PO OD, duration not specified	Placebo	SBP + DBP	MAP SBP (daily episodes ≥180mmHg) DBP (daily episodes ≥110mmHg) Length of PN hospital stay AHT requirement Urine output Maternal heart rate	
Veena 2017 <sup>19</sup>	RCT	Enrolled <24h after birth	100	24.34±4.31 24.02±4.27	Tertiary referral hospital	India	Furosemide 20mg PO OD + nifedipine 10mg PO TDS for 3 days	Nifedipine 10mg PO TDS for 3 days	SBP + DBP	MAP Maternal morbidity (postnatal complication requiring intervention) Length of hospital stay after birth Antihypertensive medication requirement Urine output	
<b>OTHER DRUGS (7 studies)</b>											
<b>Selective 5-HT antagonists</b>											
Weiner 1982 <sup>48</sup>	RCT (crossover)	F/U not specified	5	Not specified	Tertiary referral	USA	R41468 IV (dose not specified) bolus then infusion for 90min	Placebo	MAP	MAP (rate at which hypertension returned post-infusion) Urine output (infusion related diuresis)	
Weiner 1984 <sup>49</sup>	RCT (crossover)	Enrolled immediately after birth F/U 3.5h	20	28±6.4	Tertiary referral	USA	Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5min if no response.	Placebo	SBP + DBP	Maternal side effects DBP (target <95mmHg) MAP AHT requirement Response rate	
Montenegro 1985 <sup>50</sup>	RCT (crossover)	Enrolled immediately after birth F/U not specified	30	21.5 (13-31)	Tertiary referral hospital	USA	Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10min to max 12mg/hr).	Placebo	MAP	Maternal side effects	

Author and year	Methods		Participants				Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary	
<b>Alternative therapies</b>											
Hladunewich 2006 <sup>51</sup>	RCT	Enrolled immediately after birth F/U 10 days	45	29±6 28±7	Tertiary referral hospital	USA	L-arginine 3.5g PO QDS or 10g IV TDS for 3-9 days	Placebo	MAP	Maternal side effects SBP, DBP AHT requirement Laboratory values (glomerular filtration rate (GFR) (inulin clearance), Albumin/creatinine (A/C) ratio, vasoactive hormones (NO and cGMP), liver function tests (LFTs), plt) Renal plasma flow (para-amino hippurate clearance), renal blood flow = renal plasma flow / (1 - HCT), renovascular resistance	
Liu 2009 <sup>52</sup>	Quasi-randomised trial	Enrolled day 2 after birth F/U 3 weeks	72	26.6±3.7 25.7±3.9	District general hospital	China†	Shengkangbao 10g PO or IV BD for 3 weeks	No intervention	Percentage of cases with positive albuminuria	SBP, DBP Laboratory values (24h urinary albumin, plasma total protein, plasma albumin, urinary albumin negative inversion rate, renal function)	
<b>Steroids</b>											
Barrilleaux 2005 <sup>53,54</sup>	RCT	Enrolled immediately after birth F/U 4.5 days	157 (175)	24.5±6.8 23.9±6.4	Tertiary referral hospital	USA	Dexamethasone 10mg x 2, then 5mg x 2 IV BD for 48 hours	Placebo	Antihypertensive medication requirement	MAP Critical care admission Length of PN hospital stay Urine output Laboratory values (plt, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)) Stay in recovery >24h	
<b>Atrial natriuretic peptide</b>											
Shigemitsu 2015 <sup>47</sup>	Retrospective cohort study	F/U not specified	16	Not specified	Tertiary referral hospital	Japan	Carperitide (no further details)	Standard care	MAP	Maternal mortality Maternal side effects Need for dialysis Time to diuresis	
<b>UTERINE CURETTAGE (8 studies)</b>											
Salvatore 1967 <sup>58</sup>	Prospective cohort study	Enrolled immediately after birth F/U 10 days	48	16-45	Tertiary referral hospital	Brazil††	Uterine curettage	No intervention	SBP + DBP	Maternal morbidity (development of pre-eclampsia with severe features – seizures)	
Magann 1993 <sup>59</sup>	RCT	Enrolled immediately after birth F/U 24h (telephone at 7 weeks)	32	22.9±5.6 23.4±6.6	Tertiary referral hospital	USA	Uterine curettage	No intervention	MAP	Maternal side effects Length of PN hospital stay AHT requirement Urine output Laboratory values (HCT, plt, AST, LDH)	
Magann 1994 <sup>60</sup>	RCT	Enrolled immediately after birth F/U 48h (telephone at 7 weeks)	45	22.3±6.4 22.8±6.6 22.8±6.1	Tertiary referral hospital	USA	Uterine curettage	(1) Nifedipine PO OR (2) Usual care	MAP	Maternal side effects Urine output Laboratory values (HCT, plt, AST, LDH)	

Author and year	Methods		Participants				Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary	
Gocmen 1996 <sup>57</sup>	Prospective cohort study	Enrolled immediately after birth F/U 24h	50	Not specified	Tertiary referral hospital	Turkey†	Uterine curettage	No intervention	MAP	Urine output Laboratory values (plt)	
Gomez 2005 <sup>61</sup>	RCT	Enrolled immediately after birth F/U not specified	86	Not specified	Tertiary referral hospital	Peru	Uterine curettage	No intervention	MAP	Maternal side effects Length of PN hospital stay AHT requirement Urine output	
Alkan 2006 <sup>62</sup>	RCT	Enrolled immediately after birth F/U 24h	56	22.8±3.4 24.6±7.5	Tertiary referral hospital	Turkey	Uterine curettage	No intervention	MAP	Maternal side effects Urine output Laboratory values (plt, LDH, AST, ALT)	
Ragab 2013 <sup>15</sup>	RCT	Enrolled immediately after birth F/U 96h	420	Not specified	Tertiary referral hospital	Egypt	Uterine curettage	No intervention	MAP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) MAP (time to MAP ≤105mmHg) Urine output Laboratory values (creatinine, plt, UA)	
Mallapur 2015 <sup>18</sup>	RCT	Enrolled immediately after birth F/U 7 days	100	Not specified	Tertiary referral hospital	India	Uterine curettage	No intervention	MAP	Length of PN hospital stay Urine output Laboratory values (plt, renal and liver function)	
<b>ORGANISATION OF CARE (2 studies)</b>											
York 1997 <sup>26</sup>	RCT	Enrolled immediately after birth F/U 8 weeks	96 <sup>§</sup>	28±7 27±7	Tertiary referral	USA	Contact with nurse specialist; early discharge if criteria met; 2 scheduled home visits and 10 telephone calls (twice weekly for 2 weeks, then weekly for 6 weeks) during F/U	Standard care	Postnatal readmission to secondary care	Functional status Patient satisfaction Neonatal rehospitalisation / acute neonatal care Cost	
Bibbo 2014 <sup>33</sup>	Retrospective cohort study	F/U not specified (but >7 days)	138	Not specified	Tertiary referral hospital	USA	Specialised postpartum clinic	Usual care	Postnatal readmission to secondary care and triage visits	Primary care provider F/U	

§ Mixture of hypertension and diabetes – unable to separate

**APPENDIX S5: Summary of main results for included studies (n=39)****ANTIHYPERTENSIVE MEDICATIONS (18 studies)****Calcium channel blockers****BARTON 1990<sup>32</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral centres, USA**Intervention:** Nifedipine 10mg PO 4-hourly for 48 hours**Comparison:** Placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP (18-24 hours after birth)	Nifedipine group 93.9±1.6mmHg, placebo group 100.2±2.6mmHg. Difference -6.3mmHg ( $p<0.05$ ).	31 (16 intervention, 15 control); follow-up complete for all participants	Double-blind RCT; overall low risk of bias

**VERMILLION 1999<sup>21</sup>****Population:** Antenatal and postnatal women with severe pre-eclampsia or super-imposed pre-eclampsia**Setting:** Tertiary referral centres (USA)**Intervention:** Nifedipine 10mg stat PO then 20mg every 20 minutes until BP <160/110mmHg or max 5 doses (90mg) + IV placebo**Comparison:** Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or max 5 doses (300mg) + PO placebo

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP (time to target <160/100mmHg)	Nifedipine group 25.1±13.6 minutes, labetalol group 43.6±25.4 minutes. Difference -18.5 minutes ( $p=0.002$ ).	50 (21 postnatal: 10 intervention, 11 control); follow-up complete for all participants	Double-blind RCT; overall high risk of bias (other bias); small number of postnatal women (42%) (n<30); unable to obtain data for postnatal subgroup

**SAYIN 2005<sup>34</sup>****Population:** Postnatal women with pre-eclampsia, severe pre-eclampsia, superimposed pre-eclampsia or eclampsia**Setting:** Tertiary referral centres (Turkey)**Intervention:** Nifedipine 10mg PO 6-hourly until BP <150/100mmHg for 48 hours**Comparison:** Methyldopa 250mg PO 8-hourly

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP (time to target <150/100mmHg)	Nifedipine group 6.7±2.5 days; methyldopa group 8.6±5.5 days. Difference -1.9 days (NS).	83 (42 intervention, 41 control); follow-up complete for all participants	Open-label RCT; overall high risk of bias (multiple domains)

**Vasodilators****PALOT 1979<sup>36</sup>****Population:** Postnatal women with 'arterial hypertensions of labour and the postpartum period'**Setting:** Not specified (France)**Intervention:** Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose**Comparison:** Clonidine IV and furosemide 20mg IV stat

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
Maternal morbidity (development of pre-eclampsia with severe features)	Hydralazine group: no women developed eclampsia, clonidine group: 2 women developed eclampsia. No statistical analysis.	54 (11 intervention, 24 control, 19 non-systematic treatment); completeness of follow-up not specified	Retrospective cohort study; overall high risk of bias (comparability); no statistical analysis

**GRIFFIS 1989<sup>38, 39</sup>****Population:** Postnatal women with pre-eclampsia**Setting:** Tertiary referral centres (USA)**Intervention:** Hydralazine 20mg IM 6-hourly for 24h**Comparison:** Methyldopa 250mg IV 6-hourly for 24h

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP (mean at 6 and 12 hours)	6 hours: hydralazine group 104.5mmHg, methyldopa group 112mmHg. Difference -7.5mmHg ( $p=0.0057$ ). 12 hours: hydralazine group 100mmHg, methyldopa group 108mmHg. Difference -8mmHg (NS).	26 (12 intervention, 14 control); follow-up complete for all participants	Open-label RC; overall high risk of bias (multiple domains); small sample size (n<30)

**WALSS RODRIGUEZ 1991<sup>40</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Not specified (Mexico)**Intervention:** Hydralazine 40mg PO 6-hourly, duration not specified + if DBP >110mmHg PRN nifedipine 10mg sublingual every 30 minutes, to maximum of 3 doses (30mg)**Comparison:** Nifedipine 10mg sublingual every 30 minutes if DBP ≥110mmHg

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	<p><b>Primary outcome</b> SBP (mean)</p> <p><b>Treatment effect</b> Hydralazine group 143.6mmHg, nifedipine group 138.0mmHg. Difference 5.6mmHg (NS).</p> <p><b>BEGUM 2002<sup>17</sup></b> <b>Population:</b> Antenatal and postnatal women with eclampsia <b>Setting:</b> Tertiary referral centres (Bangladesh) <b>Intervention:</b> Hydralazine 5mg then 2mg IV bolus every 15 minutes until DBP 90-95mmHg <b>Comparison:</b> Hydralazine 20mg /200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15 min intervals; until DBP 90-95mmHg</p>	<p><b>Number of participants</b> 38 (18 intervention, 20 control); completeness of follow-up not specified</p>	<p><b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains)</p>
<p><b>Primary outcome</b> DBP (time to target 90-95mmHg)</p>	<p><b>Treatment effect</b> Bolus hydralazine group 65.23±23.38 minutes, hydralazine infusion group 186.36±79.77 minutes. Difference -121.13 minutes (<math>p&lt;0.001</math>).</p>	<p><b>Number of participants</b> 77 (15 postnatal: 9 intervention, 6 control); completeness of follow-up not specified</p>	<p><b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains); small number of postnatal women (19%) (n&lt;30): unable to obtain data for postnatal subgroup</p>
<p><b>VIGIL DE GRACIA 2007<sup>35</sup></b> <b>Population:</b> Postnatal women with severe gestational hypertension, severe pre-eclampsia or super-imposed pre-eclampsia <b>Setting:</b> Tertiary referral centres (Panama) <b>Intervention:</b> Hydralazine 5mg IV every 20 minutes until BP &lt;160/110mmHg or maximum 5 doses <b>Comparison:</b> Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP &lt;160/110mmHg or maximum 5 doses (300mg)</p>	<p><b>Treatment effect</b> Hydralazine group 0/42, labetalol group 1/40 (NS).</p>	<p><b>Number of participants</b> 82 (42 intervention, 40 control); follow-up complete for all participants</p>	<p><b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains)</p>
<p><b>HENNESSY 2007<sup>23</sup></b> <b>Population:</b> Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia or essential hypertension <b>Setting:</b> Tertiary referral (Australia) <b>Intervention:</b> Diazoxide 15mg IV every 3 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 300mg <b>Comparison:</b> Hydralazine 5mg IV every 20 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 15mg</p>	<p><b>Treatment effect</b> Diazoxide group 67%, hydralazine group 43% (<math>p&lt;0.01</math>). RR 0.637 (95% CI 0.46 to 0.89) for not reaching target BP with intervention.</p>	<p><b>Number of participants</b> 124 total (37 postnatal: 11 intervention, 16 control); follow-up complete for all participants</p>	<p><b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains); small proportion of postnatal women (30%): unable to obtain data for postnatal subgroup</p>
<b>Beta-blockers</b>			
<p><b>GARDEN 1982<sup>24</sup></b> <b>Population:</b> Antenatal and postnatal women with severe pre-eclampsia or eclampsia <b>Setting:</b> Tertiary referral (South Africa) <b>Intervention:</b> Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30 minutes until DBP &lt;100mmHg or maximum dose 160mg/hour <b>Comparison:</b> Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30 minutes until DBP &lt;100mmHg or maximum dose 80mg/hour</p>	<p><b>Treatment effect</b> Labetalol group 5/6, dihydralazine group 2/6. No statistical analysis.</p>	<p><b>Number of participants</b> 12 total (6 postnatal: 3 intervention, 3 control); follow-up complete for all participants</p>	<p><b>Quality of the evidence</b> RCT (blinding not specified); overall high risk of bias (other bias); very small sample size (n&lt;15): unable to obtain data for postnatal subgroup</p>
<p><b>FIDLER 1982<sup>42</sup></b> <b>Population:</b> Postnatal women with gestational hypertension <b>Setting:</b> Tertiary referral (UK) <b>Intervention:</b> Timolol 5mg PO 8-hourly for 9 days <b>Comparison:</b> Methyldopa 250mg PO 8-hourly for 9 days</p>	<p><b>Treatment effect</b> Timolol group 88.7mmHg, methyldopa group 93.8mmHg. Difference -5.1mmHg (<math>p&lt;0.05</math>).</p>	<p><b>Number of participants</b> 80 (40 intervention, 40 control); follow-up complete in 79/80 (99%)</p>	<p><b>Quality of the evidence</b> RCT (blinding not specified); overall high risk of bias (multiple domains)</p>
<p><b>MABIE 1987<sup>22</sup></b> <b>Population:</b> Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia, eclampsia or essential hypertension <b>Setting:</b> Tertiary referral (USA) <b>Intervention:</b> Labetalol 20mg IV every 10 minutes then escalating until DBP &lt;100mmHg or maximum cumulative dose reached (300mg) <b>Comparison:</b> Hydralazine 5mg IV every 10 minutes until DBP &lt;100mmHg</p>			

1	<b>Primary outcome</b> MAP (mean maximal decrease)	<b>Treatment effect</b> Labetalol group 25.5±11.2mmHg, hydralazine group 33.3±13.2mmHg. Difference -7.8mmHg ( $p=0.02$ ).	<b>Number of participants</b> 60 (41 postnatal: 27 intervention, 14 control); follow-up complete for all participants	<b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains)
2				
3	<b>SHUMARD 2016<sup>41</sup></b>			
4	<b>Population:</b> Postnatal women with gestational hypertension or pre-eclampsia			
5	<b>Setting:</b> Not specified (USA)			
6	<b>Intervention:</b> Labetalol PO (variable dose and frequency)			
7	<b>Comparison:</b> Nifedipine PO (variable dose and frequency)			
8	<b>Primary outcome</b> Length of hospital stay after delivery	<b>Treatment effect</b> Labetalol group 3.5 days, nifedipine group 3.6 days. Difference -0.1 days (NS).	<b>Number of participants</b> 128 (42 intervention, 86 control); follow-up complete for all participants	<b>Quality of the evidence</b> Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data
9				
10	<b>SHARMA 2017<sup>27 28</sup></b>			
11	<b>Population:</b> Postnatal women with gestational hypertension or pre-eclampsia			
12	<b>Setting:</b> Tertiary referral (USA)			
13	<b>Intervention:</b> Labetalol 200mg PO 12-hourly			
14	<b>Comparison:</b> Nifedipine XL 30mg PO once daily			
15	<b>Primary outcome</b> SBP + DBP (time to sustained BP control: absence of severe hypertension for $\geq 12$ hours)	<b>Treatment effect</b> Labetalol group 37.6 hours, nifedipine group 38.2 hours. Difference -0.6 hours (NS).	<b>Number of participants</b> 50 (25 intervention, 25 control); follow-up complete for all participants	<b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains)
16				
17	<b>Other antihypertensive medications</b>			
18	<b>GAISIN 2013<sup>25</sup></b>			
19	<b>Population:</b> Postnatal women with pre-eclampsia, super-imposed pre-eclampsia or essential hypertension			
20	<b>Setting:</b> Not specified (Russia)			
21	<b>Intervention:</b> Indapamide 1.5mg PO OD, duration unclear			
22	<b>Comparison:</b> Adjusted dose methyldopa			
23	<b>Primary outcome</b> SBP + DBP	<b>Treatment effect</b> Indapamide group 113±6/74±4mmHg, methyldopa group 116±5/75±4mmHg. Difference -3/+1mmHg (NS).	<b>Number of participants</b> 30 (15 intervention, 15 control); completeness of follow-up not specified	<b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data
24				
25	<b>GAISIN 2014<sup>37</sup></b>			
26	<b>Population:</b> Postnatal women with pre-eclampsia			
27	<b>Setting:</b> Not specified (Russia)			
28	<b>Intervention:</b> Indapamide 1.5mg PO once daily + ursodeoxycholic acid 250mg PO three times daily, duration unclear			
29	<b>Comparison:</b> Adjusted dose methyldopa			
30	<b>Primary outcome</b> SBP + DBP	<b>Treatment effect</b> Indapamide group 122±6/75±4 mmHg, methyldopa group 126±6/78±5mmHg. Difference -4/-3mmHg (NS).	<b>Number of participants</b> 30 (allocation not described); completeness of follow-up not specified	<b>Quality of the evidence</b> Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data; number of participants in each group not stated
31				
32	<b>KREBS 1956<sup>43 44</sup></b>			
33	<b>Population:</b> Postnatal women with gestational hypertension, pre-eclampsia, severe pre-eclampsia or eclampsia			
34	<b>Setting:</b> Not specified (Germany)			
35	<b>Intervention:</b> Reserpine 0.25mg PO or intramuscular 6-8 hourly for 7 days			
36	<b>Comparison:</b> Phenobarbital			
37	<b>Primary outcome</b> SBP + DBP (maximal reduction)	<b>Treatment effect</b> Reserpine halved time to maximal BP reduction (no further details reported). No statistical analysis.	<b>Number of participants</b> 140 (70 intervention, 70 control); completeness of follow-up not specified	<b>Quality of the evidence</b> Retrospective cohort study; overall high risk of bias (selection and outcome assessment); no statistical analysis
38				
39	<b>NORONHA NETO 2016<sup>29-31</sup></b>			
40	<b>Population:</b> Postnatal women with severe HDP			
41	<b>Setting:</b> Tertiary referral (Brazil)			
42	<b>Intervention:</b> Clonidine 0.1mg PO repeated every 20 minutes to max 6 doses			
43	<b>Comparison:</b> Captopril 25mg PO repeated every 20 minutes to max 6 doses			
44				



Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP (episodes SBP $\geq$ 180mmHg and/or DBP $\geq$ 110mmHg)	Clonidine group 2.1 $\pm$ 2.1 episodes, captopril group 3.5 $\pm$ 4.7 episodes. Difference -1.4 episodes (NS).	90 (45 intervention, 45 control); completeness of follow-up not specified	Double-blind RCT; overall low risk of bias
<b>DIURETICS (4 studies)</b>			
<b>MATTHEWS 1997<sup>46</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia or eclampsia			
<b>Setting:</b> Tertiary referral centres (UK)			
<b>Intervention:</b> Furosemide 40mg PO once daily for 7 days			
<b>Comparison:</b> Placebo			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP (decrease)	Intervention group -10.6mmHg, control group -9.75mmHg. Difference -0.85mmHg (NS).	19 (10 intervention, 9 control); follow-up complete in 18/19 (95%)	Double-blind RCT; overall high risk of bias (other bias); small sample size (n<30)
<b>ASCARELLI 2005<sup>16</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia, severe pre-eclampsia or superimposed pre-eclampsia			
<b>Setting:</b> Tertiary referral centres (USA)			
<b>Intervention:</b> Furosemide 20mg PO once daily + potassium 20mEq PO once daily for 5 days			
<b>Comparison:</b> No intervention			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP	No significant difference between groups (details not reported). Severe pre-eclampsia (n=70) day 2 SBP furosemide group 142 $\pm$ 13mmHg, usual care group 153 $\pm$ 19mmHg. Difference -11mmHg ( $p$ <0.004).	264 (132 intervention, 132 control); completeness of follow-up not specified.	Open-label RCT; overall high risk of bias (multiple domains)
<b>AMORIM 2015<sup>45</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia			
<b>Setting:</b> Tertiary referral (Brazil)			
<b>Intervention:</b> Furosemide 40mg PO once daily for maximum 5 days			
<b>Comparison:</b> Placebo			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP	Furosemide group had significantly improved SBP + DBP. Magnitude of difference not reported ( $p$ <0.001).	120 (allocation not described); follow-up complete in 118/120 (98%).	Double-blind RCT; overall high risk of bias (reporting bias); conference abstract only, authors did not provide further data; number of participants in each group not stated
<b>VEENA 2017<sup>19</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia			
<b>Setting:</b> Tertiary referral centre (India)			
<b>Intervention:</b> Furosemide 10mg PO once daily plus nifedipine 10mg PO three times daily for 3 days			
<b>Comparison:</b> Nifedipine 10mg PO three times daily for 3 days			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP	No significant difference between groups (absolute values and differences not reported, $p$ =0.457 for SBP and $p$ =0.642 for DBP).	100 (50 intervention, 50 control); follow-up complete in 98/100 (98%)	Open-label RCT; overall high risk of bias (multiple domains)
<b>OTHER DRUGS (7 studies)</b>			
<b>Selective 5-HT antagonists</b>			
<b>WEINER 1982<sup>48</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> R41468 IV (dose not specified) bolus then infusion for 90 minutes			
<b>Comparison:</b> Placebo			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP (mean maximal decline)	SSRI group -31.6mmHg, placebo group -6.0mmHg. Difference -25.6mmHg ( $p$ <0.001).	5 (crossover); follow-up complete in all participants	Double blind RCT (crossover); overall high risk of bias (other bias); conference abstract only, authors did not provide further data; very small sample size (n<15)

<b>WEINER 1984<sup>49</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia and super-imposed pre-eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5 minutes if no response.			
<b>Comparison:</b> Placebo			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
SBP + DBP (mean maximal decline)	SSRI group -41/-34mmHg, placebo group -7/-7mmHg. Difference -34/-27mmHg ( $p<0.001$ ).	20 (crossover); follow-up complete in all participants	Double blind RCT (crossover); overall high risk of bias (other bias); small sample size ( $n<30$ )
<b>MONTENEGRO 1985<sup>50</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10 minutes to max 12mg/hr).			
<b>Comparison:</b> Placebo			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
MAP	SSRI group had significantly improved MAP, over 30 minutes after drug administered. $F = 9.66$ ( $p<0.01$ )	30 (crossover); follow-up complete in 23/30 (77%)	Double blind RCT (crossover); overall high risk of bias (multiple domains)
<b>Alternative therapies</b>			
<b>HLADUNEWICH 2006<sup>51</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> L-arginine 3.5g PO four times daily OR L-arginine 10g IV three times daily (if unable to take PO) for 3-9 days postpartum			
<b>Comparison:</b> Placebo			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
MAP	Day 3: L-arginine group $102\pm 12$ mmHg, placebo group $103\pm 12$ mmHg. Difference -1mmHg (NS). Day 10: L-arginine group $98\pm 14$ mmHg, placebo group $96\pm 1$ mmHg. Difference 2mmHg (NS).	45 (22 intervention, 23 control); follow-up complete in 39/45 (87%)	Double blind RCT; overall high risk of bias (multiple domains)
<b>LIU 2009<sup>52</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia			
<b>Setting:</b> District general (China)			
<b>Intervention:</b> Shengkangbao 10g PO or IV twice daily for 3 weeks			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
Percentage of cases with positive albuminuria	3 weeks: shengkangbao group $0.7\pm 0.8\%$ positive albuminuria, usual care group $1.5\pm 0.9\%$ . Difference $-0.8\%$ ( $p<0.01$ ).	77 (allocation not described); follow-up complete in 72/77 (94%)	Open-label quasi-randomised study; overall high risk of bias (multiple domains)
<b>Steroids</b>			
<b>BARRILLEAUX 2005<sup>53,54</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia and eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> Dexamethasone 10mg x2, then 5mg x 2 IV 12-hourly for 48 hours			
<b>Comparison:</b> Placebo (IV saline)			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
Antihypertensive medication requirement	Dexamethasone group 38/77 (49%), placebo group 31/80 (39%) required antihypertensive treatment in the first 48h PN. Difference 10% (NS).	157 (77 intervention, 80 control); follow-up complete in 155/157 (99%)	Double blind RCT; overall high risk of bias (reporting bias)
<b>Atrial natriuretic peptide</b>			
<b>SHIGEMITSU 2015<sup>47</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia, HELLP syndrome or placental abruption			
<b>Setting:</b> Tertiary referral (Japan)			
<b>Intervention:</b> Carperitide (no further details supplied)			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
MAP	Carperitide group had significantly improved MAP at 48 hours. Magnitude of difference not reported, no $p$ value presented.	16 (6 intervention, 10 control); follow-up complete for all participants	Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data; small sample size ( $n<30$ )

**UTERINE CURETTAGE (8 studies)****SALVATORE 1967<sup>58</sup>****Population:** Postnatal women with severe pre-eclampsia or eclampsia**Setting:** Tertiary referral (Brazil)**Intervention:** Uterine curettage**Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP (proportion achieving target <140/90mmHg)	24 hours: curettage group 45%, usual care group 11%. No statistical analysis. 48 hours: curettage group 70%, usual care group 29%. No statistical analysis.	48 (20 intervention, 28 control); follow-up complete for all participants	Prospective cohort study; overall high risk of bias (comparability); significant differences in study groups (9/20 intervention group eclamptic at enrolment, 28/28 control group)

**MAGANN 1993<sup>59</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral (USA)**Intervention:** Uterine curettage**Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	Curettage group had significantly improved MAP to 24 hours after birth. Difference -6 to -10mmHg (16 hours $p<0.0002$ ).	32 (16 intervention, 16 control); completeness of follow-up not specified	Open-label RCT; overall high risk of bias (multiple domains)

**MAGANN 1994<sup>60</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral (USA)**Intervention:** Uterine curettage**Comparison:** Oral nifedipine OR no intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	Curettage group had significantly improved MAP 8-48 hours after birth. Difference -9 to -13mmHg ( $p=0.0017$ ). No difference between curettage and nifedipine.	45 (15 intervention, 15 each control group); completeness of follow-up not specified	Open-label RCT; overall high risk of bias (multiple domains)

**GOCMEN 1996<sup>57</sup>****Population:** Postnatal women with pre-eclampsia**Setting:** Tertiary referral (Turkey)**Intervention:** Uterine curettage**Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	Curettage group had significantly improved MAP to 24 hours after birth. Magnitude of difference not reported ( $p=0.01$ ).	50 (30 intervention, 20 control); completeness of follow-up not specified	Prospective cohort study; overall high risk of bias (comparability and outcome assessment); conference abstract only, authors did not provide further data

**GOMEZ 2005<sup>61</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral (Peru)**Intervention:** Uterine curettage**Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	Intervention group had significantly improved MAP. Time point not specified. Magnitude of difference not reported ( $p<0.001$ ).	86 (27 intervention, 59 control); completeness of follow-up not specified	Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data

**ALKAN 2006<sup>62</sup>****Population:** Postnatal women with severe pre-eclampsia**Setting:** Tertiary referral (Turkey)**Intervention:** Uterine curettage**Comparison:** No intervention

Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	24 hours: curettage group 103.4±7.8mmHg, usual care group 110.2±4.8. Difference -6.8mmHg ( $p<0.05$ ).	56 (31 intervention, 25 control); follow-up complete for all participant	Open-label RCT; overall high risk of bias (multiple domains)

<b>RAGAB 2013<sup>15</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia or eclampsia			
<b>Setting:</b> Tertiary referral (Egypt)			
<b>Intervention:</b> Uterine curettage			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
MAP	6 hours: curettage group 140.1±6.12mmHg, usual care group 152.4±3.7mmHg. Difference -12.3mmHg ( $p=0.02$ ). 24 hours: curettage group 101.4±7.14mmHg, usual care group 110.6±2.22mmHg. Difference -9.2mmHg ( $p=0.01$ ).	420 (220 intervention, 200 control); follow-up complete for all participants	Open-label RCT; overall high risk of bias (multiple domains)
<b>MALLAPUR 2015<sup>18</sup></b>			
<b>Population:</b> Postnatal women with severe pre-eclampsia or eclampsia			
<b>Setting:</b> Tertiary referral (India)			
<b>Intervention:</b> Uterine curettage			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
MAP	From 4 hours after birth: curettage group 116±4.4mmHg, usual care group 123.6±6.1mmHg. Difference -7.6mmHg ( $p<0.001$ ).	100 (50 intervention, 50 control); completeness of follow-up not specified	Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data
<b>ORGANISATION OF CARE (2 studies)</b>			
<b>YORK 1997<sup>26</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia or essential hypertension, or diabetes			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> Nurse specialist follow-up			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
Postnatal readmission to secondary care	No significant difference between groups.	96 (44 intervention, 52 control); completeness of follow-up not specified	Open-label RCT; overall high risk of bias (multiple domains); population mixed diabetes and/or hypertension – unable to separate
<b>BIBBO 2014<sup>33</sup></b>			
<b>Population:</b> Postnatal women with pre-eclampsia			
<b>Setting:</b> Tertiary referral (USA)			
<b>Intervention:</b> Specialised postpartum clinic			
<b>Comparison:</b> No intervention			
<b>Primary outcome</b>	<b>Treatment effect</b>	<b>Number of participants</b>	<b>Quality of the evidence</b>
Postnatal readmission to secondary care and triage visits	Clinic group 21.7%, usual care group 8.7%. Difference 13% ( $p<0.039$ ).	138 (69 intervention, 69 control); completeness of follow-up not specified.	Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data

**Appendix S6: Risk of bias in included studies (n=38)****Appendix S6a: Risk of bias in included RCTs and quasi-randomised studies (n=31)**

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
<b>ANTIHYPERTENSIVE MEDICATIONS</b>							
Fidler 1982 <sup>42</sup>	Unclear	Unclear	Unclear	Unclear	High	High	Low
Garden 1982 <sup>24</sup>	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Mabie 1987 <sup>22</sup>	Unclear	Unclear	High	High	Low	Low	High
Griffis 1989 <sup>38,39</sup>	Unclear	Low	High	High	High	High	High
Barton 1990 <sup>32</sup>	Low	Low	Low	Low	Low	Low	Low
Walss Rodriguez 1991 <sup>40</sup>	Low	Low	High	High	Unclear	Unclear	Low
Vermillion 1999 <sup>21</sup>	Low	Low	Low	Low	Low	Low	High
Begum 2002 <sup>17</sup>	High	High	High	High	Unclear	Unclear	High
Sayin 2005 <sup>34</sup>	Unclear	Unclear	High	High	Low	Unclear	High
Hennessy 2007 <sup>23</sup>	Unclear	Low	High	High	Low	Low	High
Vigil-de-Gracia 2007 <sup>35</sup>	Low	Low	High	High	Low	Low	Low
Gaisin 2013 <sup>25</sup>	Unclear	Unclear	High	High	Unclear	High	High
Gaisin 2014 <sup>37</sup>	Unclear	Unclear	High	High	Unclear	Unclear	High
Noronha Neto 2016 <sup>29-31</sup>	Low	Low	Low	Unclear	Low	Low	Low
Sharma 2017 <sup>27,28</sup>	Low	Low	High	High	Unclear	Low	Low
<b>DIURETICS</b>							
Matthews 1997 <sup>46</sup>	Unclear	Low	Low	Low	Low	Unclear	High
Ascarelli 2005 <sup>16</sup>	Unclear	Low	High	High	Unclear	High	Low
Amorim 2015 <sup>45</sup>	Low	Low	Low	Low	Low	High	Low
Veena 2017 <sup>19</sup>	Low	Low	High	High	Unclear	Unclear	Unclear
<b>OTHER DRUGS</b>							
Weiner 1982 <sup>48</sup>	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Weiner 1984 <sup>49</sup>	Low	Unclear	Low	Low	Low	Unclear	High
Montenegro 1985 <sup>50</sup>	Unclear	Unclear	Low	Low	High	High	High
Barrilleaux 2005 <sup>53,54</sup>	Low	Low	Low	Low	Low	High	High
Hladunewich 2006 <sup>51</sup>	Low	Low	Low	Low	High	High	High
Liu 2009 <sup>52</sup>	High	High	High	High	High	Unclear	High
<b>UTERINE CURETTAGE</b>							
Magann 1993 <sup>59</sup>	Low	Low	High	High	Unclear	Unclear	Low
Magann 1994 <sup>60</sup>	Low	Unclear	High	High	Unclear	Unclear	Low
Gomez 2005 <sup>61</sup>	Unclear	Unclear	High	High	Unclear	High	Low
Alkan 2006 <sup>62</sup>	Unclear	Unclear	High	High	Low	High	High
Ragab 2013 <sup>15</sup>	Low	Low	High	High	Low	Low	Low
Mallapur 2015 <sup>18</sup>	Low	Unclear	High	High	Unclear	Unclear	High
<b>ORGANISATION OF CARE</b>							
York 1997 <sup>26</sup>	Unclear	Low	High	High	Unclear	Unclear	High

## Appendix S6b: Risk of bias in included cohort studies (n=7)

Study ID	Selection				Comparability <sup>1</sup>	Outcome		
	Representative-ness <sup>2</sup>	Selection of non-exposed <sup>3</sup>	Ascertainment of exposure <sup>4</sup>	Outcome of interest not present at start		Assessment <sup>5</sup>	F/U long enough	Adequacy of F/U <sup>6</sup>
<b>ANTIHYPERTENSIVE MEDICATIONS</b>								
Krebs 1956 <sup>43 44</sup>	Low (a)	Low (a)	Unclear (d)	Low (Yes)	Low (a)	High (b)	Low (Yes)	Unclear (d)
Palot 1979 <sup>36</sup>	Unclear (d)	Low (a)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)
Shumard 2016 <sup>41</sup>	Low (a)	Low (a)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
<b>OTHER DRUGS</b>								
Shigemitsu 2015 <sup>47</sup>	Unclear (d)	Unclear (c)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Unclear (d)
<b>UTERINE CURETTAGE</b>								
Salvatore 1967 <sup>58</sup>	High (b)	High (b)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
Gocmen 1996 <sup>57</sup>	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	High (No)	Unclear (d)
<b>ORGANISATION OF CARE</b>								
Bibbo 2014 <sup>33</sup>	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)

<sup>1</sup> (a) study controls for most important factor; (b) study controls for any additional factor

<sup>2</sup> (a) truly representative of the average in the community; (b) somewhat representative of the average in the community; (c) selected group of users e.g. nurses, volunteers; (d) no description of the derivation of the cohort

<sup>3</sup> (a) drawn from the same community as the exposed cohort; (b) drawn from a different source; (c) no description of the derivation of the non-exposed cohort

<sup>4</sup> (a) secure record (e.g. surgical record); (b) structured interview; (c) written self-report; (d) no description

<sup>5</sup> (a) independent blind assessment; (b) record linkage; (c) self-report; (d) no description

<sup>6</sup> (a) complete follow-up; (b) subjects lost to follow-up unlikely to introduce bias (>90% follow-up rate); (c) follow up rate <90% and no description of those lost; (d) no statement