



Hypertension in pregnancy: Evidence Update May 2012

A summary of selected new evidence relevant to NICE clinical guideline 107 'The management of hypertensive disorders during pregnancy' (2010)



Evidence Update 16

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/hypertension). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

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Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

 ¹ **Hypertension in pregnancy. NICE clinical guideline 107 (2010). Available from www.nice.org.uk/guidance/CG107**

A search was conducted for new evidence published between 20 May 2009 and 14 December 2011. Nearly 800 pieces of evidence were identified and assessed, of which 14 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

¹ NICE-accredited guidance is denoted by the Accreditation Mark 

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Key message	Effect on guidance	
	Potential change	No change
<p>Reducing the risk of hypertensive disorders in pregnancy</p> <ul style="list-style-type: none"> Evidence for potential biochemical and ultrasound markers is unlikely to affect current advice on identifying women likely to be at high risk of hypertensive disorders during pregnancy. Evidence is consistent with the current guidance that women at moderate or severe risk of pre-eclampsia should take aspirin² daily from 12 weeks until birth of the baby. There is insufficient evidence currently to change the recommendation that women should not receive nitric oxide donors or heparin to prevent hypertensive disorders. Evidence shows that antioxidant vitamins (vitamins C and E) are not effective at preventing hypertensive disorders, supporting the current recommendation that they should not be used in pregnancy. 		<p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p>
<p>Management of pregnancy with chronic hypertension</p> <ul style="list-style-type: none"> Limited evidence for the benefit of nicardipine³ in severe chronic hypertension during pregnancy is unlikely to affect current guidance. 		<p>✓</p>
<p>Management of pregnancy with gestational hypertension</p> <ul style="list-style-type: none"> Limited evidence for the benefit nicardipine³ in severe gestational hypertension is unlikely to affect current guidance. Evidence supports the current recommendation that induction of labour should not be routinely offered before 37 weeks, but suggests that induction after 37 weeks is not more costly than expectant management. 		<p>✓</p> <p>✓</p>

² At the time of publication of this Evidence Update, aspirin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

³ Nicardipine is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for this indication.

Key message	Effect on guidance	
	Potential change	No change
<p>Management of pregnancy with pre-eclampsia</p> <ul style="list-style-type: none"> • Evidence supports the current recommendation that quantification of proteinuria in women with pre-eclampsia does not need to be repeated once 'significant proteinuria' has been confirmed. • Evidence supports the current recommendation that induction of labour should not be routinely offered before 37 weeks, but suggests that induction after 37 weeks is not more costly than expectant management. • Evidence supports the current recommendation to manage pregnancies conservatively before 34 weeks of gestation if possible. 		<p>✓</p> <p>✓</p> <p>✓</p>
<p>Intrapartum care</p> <ul style="list-style-type: none"> • Evidence for the benefit of remifentanyl⁴ patient-controlled analgesia compared with epidural analgesia during labour in women with pre-eclampsia is currently limited and larger trials are needed. 		<p>✓</p>
<p>Medical management of severe hypertension or severe pre-eclampsia in a critical care setting</p> <ul style="list-style-type: none"> • Evidence supports current recommendations that corticosteroids should not be used for the treatment of HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, though use to increase platelets when clinically required may be justified. 		<p>✓</p>
<p>Advice and follow-up care at transfer to community care</p> <p><i>Risk of recurrence of hypertensive disorders of pregnancy</i></p> <ul style="list-style-type: none"> • Recent evidence assessing the value of predictive tests for risk of hypertensive disorders in a subsequent pregnancy is unlikely to affect current guidance. 		<p>✓</p>

⁴ Remifentanyl is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for this indication.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided. Section headings are taken from the guidance.

1.1 Reducing the risk of hypertensive disorders in pregnancy

Risk factors

[NICE clinical guideline \(CG\) 107](#) identifies women at high risk of pre-eclampsia as those with previous hypertensive disorder during pregnancy, chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, diabetes or chronic hypertension. A systematic review by [Giguère et al. \(2010\)](#) assessed 71 different combinations of biochemical and ultrasonographic markers to predict the risk of pre-eclampsia in pregnant women, from data in 37 studies (number of women involved not reported). Most markers evaluated were identified during the second trimester on small populations of women already identified as at high risk, and would, therefore, be recommended to receive aspirin from week 12 to birth. In a low risk population combining markers generally increased sensitivity and/or specificity compared with single markers. Combinations including level of placental protein 13, pregnancy-associated plasma protein A, a disintegrin and metalloprotease-12, activin A, or inhibin A measured in first or early second trimester and uterine artery Doppler in second trimester resulted in sensitivity of 60–80% and specificity above 80%. The authors note the need for further studies in large populations before such approaches could be used for screening purposes to identify pregnant women at risk. This evidence is unlikely to affect current recommendations for identification of women at high risk of hypertensive disorders of pregnancy given in NICE CG107.

Key reference

Giguère Y, Charland M, Bujold E et al. (2010) Combining biochemical and ultrasonic markers in predicting preeclampsia: a systematic review. *Clinical Chemistry* 56: 361–74
Full text: www.clinchem.org/content/56/3/361.full.pdf+html

Antiplatelet agents

[NICE CG107](#) recommends that women at moderate or high risk of pre-eclampsia are advised to take aspirin 75 mg/day from 12 weeks until the birth of the baby. Aspirin did not have UK marketing authorisation for this indication at the time of publication of this Evidence Update. Informed consent should be obtained and documented.

A systematic review and meta-analysis by [Bujold et al. \(2010\)](#) estimated the effect of low-dose aspirin (50–150 mg/day alone or in combination with dipyridamole or other antiplatelet agents) started early in pregnancy on the incidence of pre-eclampsia in 27 randomised controlled trials (RCT) involving 11,348 women at risk of pre-eclampsia. Starting treatment at 16 weeks or earlier significantly reduced the incidence of pre-eclampsia compared with placebo or no treatment (relative risk [RR] = 0.47; 95% confidence interval [CI] 0.34 to 0.65; 9.3% of treated women compared with 21.3% of controls). There was also a reduction in risk of severe pre-eclampsia (RR = 0.09; 95% CI 0.02 to 0.37; 0.7% of treated women compared with 15.0% of controls), gestational hypertension (RR = 0.62; 95% CI 0.45 to 0.84; 16.7% of treated women compared with 29.7% of controls) and preterm birth (RR = 0.22; 95% CI 0.10 to 0.49; 3.5% of treated women compared with 16.9% of controls).

Low-dose aspirin treatment started after 16 weeks of gestation did not result in a statistically significant difference in risk of pre-eclampsia compared with placebo or no treatment (RR = 0.81; 95% CI 0.63 to 1.03; 7.3% of treated women compared with 8.1% of controls). An effect of gestational age was also seen with regard to the impact of low-dose aspirin

therapy on intrauterine growth restriction, with a significant effect when treatment was given on or before 16 weeks (RR = 0.44; 95% CI 0.30 to 0.65; 7% of treated women compared with 16.3% of controls) but not when given after 16 weeks (RR = 0.98; 95% CI 0.87 to 1.10; 10.3% of treated women compared with 10.5% of controls).

The authors noted that all studies starting aspirin therapy at 16 weeks or earlier included women at moderate or high risk of pre-eclampsia; a funnel plot and sensitivity analysis suggested publication bias which may limit the strength of any conclusions. Trials included in the analysis dated from 1985 to 2005, and evidence from these was considered during development of NICE CG107.

A systematic review by [Duley \(2011\)](#) reported no difference in the impact of aspirin prophylaxis before and after 20 weeks gestation. The review included a total of 69 systematic reviews, RCTs or observational studies. Evidence considered to be high quality from a systematic review using aggregate data (59 RCTs; 37,560 women) and a systematic review using data from individual patients (31 RCTs; 32,217 women) confirmed that antiplatelet drugs (primarily low-dose aspirin) reduce the risk of pre-eclampsia, death of the baby and premature birth, without increasing the risks of bleeding in women at high risk of pre-eclampsia. The review also examined the effect of other interventions to prevent pre-eclampsia, treat mild to moderate hypertension, treat severe episodes of pre-eclampsia and use of anticonvulsants in eclampsia. The original RCTs included in these reviews were considered during development of [NICE CG107](#), given the search date of 2006.

This evidence is consistent with the advice of NICE CG107 for women at moderate or high risk of pre-eclampsia to take aspirin 75 mg/day from 12 weeks until the birth of the baby, though it is not clear from the meta-analysis by Bujold et al. (2010) at what gestational age administration of aspirin 75 mg daily to women at high-risk of pre-eclampsia becomes of minimal value.

Current recommendations are unlikely to be amended without further research to determine the optimal timing and dose of treatment, and any associated implications for service delivery.

Key references

[Bujold E, Roberge S, Lacasse Y et al. \(2010\) Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy. *Obstetrics & Gynecology* 116: 402–12](#)

Abstract: www.greenjournal/Abstract/2010/08000

[Duley L \(2011\) Pre-eclampsia, eclampsia, and hypertension. *Clinical Evidence* 2: 1402](#)

Abstract: www.ncbi.nlm.nih.gov/pubmed/21718554

Other pharmaceutical agents

[NICE CG107](#) advises that nitric oxide donors, progesterone, diuretics and low molecular weight heparin are not used to prevent hypertensive disorders during pregnancy. Recent evidence supports this recommendation.

Two RCTs ([Neri et al. 2010](#); [Vadillo-Ortega et al. 2011](#)) studied the effect of L-arginine during pregnancy, a possible source of substrate for nitric oxide synthesis. In the study by Neri and colleagues, 80 pregnant women with mild chronic hypertension (defined as systolic blood pressure \geq 140 mmHg and \leq 160 mmHg or diastolic blood pressure \geq 90 mmHg and \leq 110 mmHg on two occasions at least 4 hours apart before week 20 of gestation) were randomised to receive oral supplementation with L-arginine 4 g/day or placebo. There was no difference between groups in blood pressure change after 10–12 weeks of treatment, though no power calculation was reported. Fewer women receiving supplementation received antihypertensive drugs (24% compared with 45%; $p < 0.05$).

In the study by Vadillo-Ortega et al. (2011) women in Mexico at high risk of pre-eclampsia (previous pregnancy complicated by pre-eclampsia or pre-eclampsia in a first degree relative)

were randomised to receive food bars containing L-arginine with antioxidant vitamins (n = 228), bars with just antioxidant vitamins (n = 222) or placebo bars without L-arginine or antioxidant vitamins (n = 222). The intervention started from 14 weeks (mean 20 weeks gestation) and continued until birth. Compared to control, there was a significant reduction in pre-eclampsia or eclampsia in the group receiving both L-arginine and antioxidant vitamins (RR = 0.42; 95% CI 0.28 to 0.62; p < 0.001). The trial was not sufficiently large to assess safety issues and focused on a single high risk group. Furthermore, L-arginine alone was not tested in this study.

Nitric oxide levels were not assessed in either study. Further research would be required before such supplementation could be considered in future reviews of guidance.

Heparin was among the antithrombotic treatments considered in a Cochrane review by [Dodd et al. \(2010\)](#) of women considered at risk of placental dysfunction. Five RCTs involving 484 women compared heparin (low molecular weight or unfractionated heparin, alone or in combination with dipyridamole) with no treatment (four studies), and trapidil (triazolopyrimidine) with placebo (one study). Following heparin treatment there were no statistically significant differences for the primary outcomes (perinatal mortality, preterm birth at less than 34 weeks of gestation, and major neurodevelopmental handicap at childhood follow up [length of follow up not stated]). None of the primary outcomes were reported in the study with trapidil. This evidence is consistent with the current recommendation of [NICE CG107](#) not to use heparin.

The secondary outcomes studied suggested some benefits of treatment. Women receiving heparin were less likely to experience pre-eclampsia (RR = 0.23; 95% CI 0.08 to 0.68; two studies; 100 women) or eclampsia (RR = 0.13; 95% CI 0.02 to 0.97; one study; 110 women) and their infants were less likely to have birth weight below the 10th centile (RR = 0.35; 95% CI 0.20 to 0.64; four studies; 319 infants). The authors noted the small number of studies and participants contributing information to the analysis, and identified a need for more information about adverse outcomes for infants and long-term childhood outcomes. Further RCTs of sufficient size are needed to examine these issues.

Key references

Dodd JM, McLeod A, Windrim RC et al. (2010) Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. Cochrane Database of Systematic Reviews issue 6: CD006780
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD006780.pub2/pdf

Neri I, Monari F, Sgarbi L et al. (2010) L-arginine supplementation in women with chronic hypertension: impact on blood pressure and maternal and neonatal complications. *Journal of Maternal-Fetal and Neonatal Medicine* 23: 1456–60
Abstract: www.informahealthcare.com/doi/abs/10.3109/14767051003677962

Vadillo-Orega F, Perichart-Perera O, Espino S et al. (2011) Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *British Medical Journal* 342: d2901
Full text: www.bmj.com/content/342/bmj.d2901

Nutritional supplements

[NICE CG107](#) advises that antioxidants (vitamins C and E) and other nutritional supplements are not recommended solely with the aim of preventing hypertensive disorders during pregnancy. Recent evidence from a systematic review and meta-analysis by [Basaran et al. \(2010\)](#) of nine RCTs (19,675 pregnant women) suggests that vitamin C and E supplementation is not only ineffective in preventing hypertensive disorders during pregnancy, but raises some concerns that it may be harmful. Among the studies included in the review were three newly reported RCTs that were not considered during development of NICE CG107.

The review reported no difference in the risk of pre-eclampsia between women receiving vitamins C and E and those receiving placebo (RR = 0.98; 95% CI 0.87 to 1.10; 9.7% of treated women compared with 9.5% of controls). There appeared to be an increased risk of gestational hypertension (RR = 1.11; 95% CI 1.05 to 1.17; 22.6% of women receiving vitamin supplementation compared with 20.3% of controls) but decreased risk of placental abruption (RR = 0.67; 95% CI 0.46 to 0.98; 0.58% of treated women compared with 0.87% of controls). The authors noted that these associations may not be causal as they are the result of multiple statistical comparisons and the confidence intervals are close to one.

Key reference

Basaran A, Basaran M, Topatan B (2010) Combined vitamin C and E supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. *Obstetrical & Gynecological Survey* 65: 653–67

Abstract: www.journals.lww.com/obgynsurvey/Abstract/2010

1.2 Management of pregnancy with chronic hypertension

Treatment of hypertension

[NICE CG107](#) recommends that women with chronic hypertension are offered antihypertensive treatment dependent on pre-existing treatment, side-effect profiles and teratogenicity.

A systematic review by [Nij Bijvank and Duvekot \(2010\)](#) included five studies of nicardipine in 147 pregnant women (> 20 weeks of gestation) with severe (mean diastolic blood pressure above 110 mmHg) chronic or gestational hypertension with or without proteinuria. Three of the studies were observational and included 20–30 women, one study was a retrospective study of 50 women and one study of 60 women was an RCT comparing nicardipine and labetalol therapy. The dose of nicardipine used in one study was 2, 4 or 6 mg/hour, and in another study reported as 20–80 mg/day; no dose information was given in the other studies. All studies reported a significant reduction in diastolic and systolic blood pressure with nicardipine treatment, with 3–21% of patients achieving at least a 20% reduction in blood pressure in the three studies reporting this outcome. No severe maternal or fetal side effects were reported in these five studies.

The evidence from Nij Bijvank and Duvekot (2010) is unlikely to affect current guidance as the size and design of the studies precluded detailed analysis of outcomes. Further prospective RCTs are required to establish efficacy and safety outcomes of nicardipine in pregnant women with chronic hypertension. Nicardipine is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for this indication.

Key reference

Nij Bijvank SWA, Duvekot JJ (2010) Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature. *Obstetrical & Gynecological Survey* 65: 341–7

Abstract: www.journals.lww.com/obgynsurvey/Abstract/2010/05000

1.3 Assessment of proteinuria in hypertensive disorders of pregnancy

No new key evidence was found for this section.

1.4 Management of pregnancy with gestational hypertension

Treatment of hypertension

[NICE CG107](#) recommends first-line treatment with oral labetalol for severe hypertension in women with gestational hypertension. Labetalol is licensed for the treatment of hypertension, including during pregnancy. The British National Formulary advises that the use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester, and breastfeeding infants should be monitored as there is a risk of possible toxicity due to alpha- and beta-blockade. Informed consent on the use of labetalol in these situations should be obtained and documented.

A systematic review by [Nij Bijvank and Duvekot \(2010\)](#) included five studies of nicardipine treatment for severe hypertension in 147 pregnant women with chronic or gestational hypertension with or without proteinuria (see 'Treatment of hypertension' in section 1.2 for details). The evidence from this review is unlikely to affect current guidance as the size and design of the studies precluded detailed analysis of outcomes. Further prospective RCTs are required to establish efficacy and safety outcomes of nicardipine in gestational hypertension. Nicardipine is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for this indication.

Timing of birth

An economic analysis of a Dutch RCT (HYPITAT: Hypertension and Pre-eclampsia Intervention Trial At Term) was reported by [Vijgen et al. \(2010\)](#). Findings from the clinical analysis of the trial, reported by [Koopmans et al. \(2009\)](#), were considered during development of [NICE CG107](#). The multicentre, unblinded study compared outcomes after induction of labour and expectant monitoring in 756 pregnant women (36–41 weeks' gestation) with gestational hypertension (diastolic blood pressure ≥ 95 mmHg on two occasions at least 6 hours apart) or mild pre-eclampsia (diastolic blood pressure ≥ 90 mmHg on two occasions at least 6 hours apart and proteinuria). The study found that induction of labour after 37 weeks reduced the risk of poor maternal outcomes (maternal mortality, maternal morbidity, progression to severe hypertension or proteinuria, major post-partum haemorrhage) compared with expectant monitoring (RR = 0.71; 95% CI 0.59 to 0.86; $p < 0.0001$). There was no difference in rate of caesarean section between induction and control group (RR = 0.75; 95% CI 0.55 to 1.04; $p = 0.085$; 14% vs 19%). Induction after 37 weeks was less costly than expectant monitoring (average cost per woman €7077 vs €7908), primarily because of reduced costs during the antepartum period in those with induced labour (average cost per woman €1259 vs €2700). Sensitivity analyses did not include the impact of a potential increased rate of caesarean section in patients undergoing induction of labour.

NICE CG107 recommends that birth is not offered before 37 weeks to women with gestational hypertension (blood pressure lower than 160/110 mmHg). The economic analysis of HYPITAT supports this guidance, and provides reassurance that induction after this date is not more costly than expectant monitoring, if the rate of caesarean section is not increased.

Key reference

Vijgen SMC, Koopmans CM, Opmeer BC et al. (2010) An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT). *BJOG An International Journal of Obstetrics and Gynaecology* 117: 1577–85
Full text: www.onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2010.02710.x/full

Supporting reference

Koopmans CM, Bijlenga D, Groen H et al. (2009) Induction of labour versus expectant monitoring for gestational hypertension of mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 374: 979–88

Abstract: [www.thelancet.com/journals/lancet/6736\(09\)60736-4/abstract](http://www.thelancet.com/journals/lancet/6736(09)60736-4/abstract)

1.5 Management of pregnancy with pre-eclampsia

Treatment of hypertension

A systematic review by [Thangaratinam et al. \(2009\)](#) of 16 studies (6749 women) showed that proteinuria is a poor predictor of complications in women with pre-eclampsia. For a threshold level of 5 g/24 hours, the likelihood ratios of positive and negative tests for stillbirths were 2.0 (95% CI 1.5 to 2.7) and 0.53 (95% CI 0.27 to 1), for neonatal deaths were 1.5 (95% CI 0.94 to 2.4) and 0.73 (95% CI 0.39 to 1.4), and for admission to neonatal intensive care were 1.5 (95% CI 1 to 2) and 0.78 (95% CI 0.64 to 0.95). This evidence supports [NICE CG107](#), which notes that quantification of proteinuria in women with pre-eclampsia does not need to be repeated after confirmation of 'significant proteinuria' (that is, a urinary protein:creatinine ratio greater than 30 mg/mmol or a validated 24-hour urine collection result showing greater than 300 mg protein).

Key reference

Thangaratinam S, Coomarasamy A, O'Mahony F et al. (2009) Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. *BMC Medicine* 7: 10

Full text: www.biomedcentral.com/1741-7015/7/10

Timing of birth

The HYPITAT study of induction of birth after 37 weeks, reported by [Vijgen et al. \(2010\)](#), included women with mild pre-eclampsia (for discussion of these findings, see 'Timing of birth' in section 1.4). Evidence supports the current recommendation that induction of labour should not be routinely offered before 37 weeks, but suggests that induction after 37 weeks is not more costly than expectant management.

A systematic review by [Magee et al. \(2009\)](#) compared outcomes associated with expectant and interventionist care of women with severe preeclampsia before 34 weeks of gestation, reported in 72 publications (observational studies or RCTs with relevant treatment arms, which were treated as separate cohorts). Most studies were conducted in tertiary centres in the developed world. Findings from the studies were synthesised to provide median and interquartile ranges (IQR) for categorical outcomes. Expectant care was associated with greater pregnancy prolongation (reported as mean time to delivery 11.3 days, IQR 8.0 to 14.4 days; reported as median time to delivery 7.7 days, IQR of 5 to 10 days; 39 cohorts, 4650 women) compared with interventionist care (reported as mean time to delivery 2.2 days, IQR 1.8 to 2.5; 2 studies, 42 women). In developed world sites, there was no difference in rates of stillbirth with the two approaches (both median 0, IQR 0 to 0). However, the neonatal death rate appeared higher with interventionist care (12.5%, IQR 9.8% to 15.2%) than expectant care (7.3%, IQR 5.0% to 10.7%). The evidence in this review supports the recommendations of [NICE CG107](#) to maintain pregnancy in women with pre-eclampsia conservatively until 34 weeks of gestation when possible.

Key reference

Magee LA, Yong PJ, Espinosa V et al. (2009) Expectant management of severe preeclampsia remote from term: a structured systematic review. *Hypertension in Pregnancy* 28: 312–47

Abstract: www.informahealthcare.com/doi/abs/10.1080/10641950802601252

1.6 Fetal monitoring

No new key evidence was found for this section.

1.7 Intrapartum care

Analgesia

[NICE CG107](#) recommends that women with severe pre-eclampsia should not receive preloading with intravenous fluids before regional analgesia during labour. Evidence on alternative methods of intrapartum analgesia in women with pre-eclampsia is limited.

An RCT by [El-Kerdawy and Farouk \(2010\)](#) compared outcomes in women with pre-eclampsia following intrapartum epidural analgesia (n = 15) or by patient-controlled analgesia with intravenous remifentanyl (n = 15). There were no significant differences in the level of analgesia, as assessed by visual analogue pain score (for example, 1 hour after delivery: 2.6 ± 1.5 with epidural vs 3 ± 1 with remifentanyl), or sedation level, as assessed on a scale of 1 to 4 (for example, 1 hour after delivery: 1.1 ± 0.35 with epidural vs 1.3 ± 0.48 with remifentanyl). In the neonates, there were no significant differences in Apgar score (score ≤ 7 in one infant in each group after 1 minute, and no babies in either group after 5 minutes). There was no significant difference between epidural and remifentanyl analgesia in terms of nausea (seven women vs five women respectively) and vomiting (two women vs one woman respectively), however epidural analgesia was associated with more (p < 0.05) itching (three women vs one woman) and hypotension (four women vs no women).

Limitations of the evidence included no reporting of the randomisation method and the absence of a power calculation. An RCT of 30 patients is too limited in size to draw firm conclusions about the efficacy or safety of remifentanyl. This evidence is unlikely to affect NICE CG107 and larger trials are needed.

A meta-analysis by [Schnabel et al. \(2012\)](#) (although not specifically in women with pre-eclampsia) found that epidural analgesia provided superior pain relief in comparison with remifentanyl. However, as remifentanyl may offer potential benefits in reducing risk of hypertension, further research into its use during labour specifically in women with pre-eclampsia may be warranted. Remifentanyl is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for this indication.

Key reference

El-Kerdawy H, Farouk A (2010) Labor analgesia in preeclampsia: remifentanyl patient controlled intravenous analgesia versus epidural analgesia. *Middle East Journal of Anesthesiology* 20: 539–44
Full text: www.meja.aub.edu.lb/downloads/20_4/P539.pdf

Supporting reference

Schnabel A, Hahn N, Borscheit J et al. (2012) Remifentanyl for labour analgesia: a meta-analysis of randomised controlled trials. *European Journal of Anaesthesiology* doi:10.1097/EJA.0b013e32834fc260
Abstract:
www.journals.lww.com/ejanaesthesiology/pages/articleviewer.aspx?year=2012&issue=04000&article=0004&type=abstract

1.8 Medical management of severe hypertension or severe pre-eclampsia in a critical care setting

Corticosteroids to manage HELLP syndrome

A Cochrane review by [Woudstra et al. \(2010\)](#) examined the effects of corticosteroids on women with HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome in pregnancy. A total of 11 RCTs (550 women) was included, comparing corticosteroid use with placebo, no treatment, other drugs or alternative corticosteroid or corticosteroid dose regimen. There were no significant differences between treatment and control for maternal death (RR = 0.95; 95% CI 0.28 to 3.21), maternal death/severe maternal morbidity (RR = 0.27; 95% CI 0.03 to 2.12) or perinatal/infant death (RR = 0.64; 95% CI 0.21 to 1.97). Treatment improved platelet count (standardised mean difference [MD] = 0.67; 95% CI 0.24 to 1.0), with the effect most pronounced for women receiving antenatal treatment (standardised MD = 0.80; 95% CI 0.25 to 1.35). With regard to platelet count, but not clinical outcomes, dexamethasone treatment was more effective than betamethasone (MD = 6.02; 95% CI 1.71 to 10.33; two studies; 76 women).

The authors concluded there was insufficient evidence of benefits on important clinical outcomes to support the use of steroids for the management of HELLP, consistent with the recommendation of [NICE CG107](#) not to use corticosteroids for HELLP syndrome.

Key reference

Woudstra DM, Chandra S, Hofmeyr GJ et al. (2010) Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. *Cochrane Database of Systematic Reviews* issue 9: CD008148

Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD008148.pub2/pdf

1.9 Breast-feeding

No new key evidence was found for this section.

1.10 Advice and follow-up care at transfer to community care

Risk of recurrence of hypertensive disorders of pregnancy

As noted in [NICE CG107](#), women with a history of gestational hypertension or pre-eclampsia are at increased risk of recurrence of hypertensive disorders in future pregnancies. A systematic review by [Sep et al. \(2010\)](#) assessed the efficacy of 24 prediction tests identified in 33 studies, ranging in size from 23 to 20,285 women with a history of hypertensive disorders during a previous pregnancy. Few single factors were found to predict the risk of recurrent hypertensive disease in pregnancy with both high sensitivity and specificity. Three tests showed reasonable predictive capacity with both sensitivity and specificity considerably higher than 50%: low plasma volume predicting gestational hypertension (sensitivity = 100%; specificity = 74%; positive likelihood ratio [LR+] = 3.83; negative likelihood ratio [LR-] = 0.003) or pre-eclampsia (sensitivity = 83%; specificity = 100%; LR+ = 58.15; LR- = 0.20) in women with previous pre-eclampsia; high resistance index (> 0.58) and the presence of early diastolic notch in the uterine arteries at 24 weeks gestation predicting gestational hypertension (respectively, sensitivity = 89% and 78%; specificity = 66% and 70%; LR+ = 2.61 and 2.61; LR- = 1.17 and 0.32) and fetal growth restriction (respectively, sensitivity = 85% and 85%; specificity = 70% and 77%; LR+ = 2.80 and 3.64; LR- = 0.22 and 0.20) after previous pre-eclampsia; and a multivariable model including longitudinal in-pregnancy patterns predicting recurrent pre-eclampsia (sensitivity = 79%; specificity = 89%; LR+ = 6.88; LR- = 0.24). These tests required frequent use so have limited practical application. This evidence is unlikely to affect recommendations for the management of

women with a history of hypertensive disorders during pregnancy, who are considered at high risk of pre-eclampsia and would, therefore, be recommended to receive aspirin from 12 weeks until birth.

Key reference

Sep S, Smits L, Prins M et al. (2010) Prediction tests for recurrent hypertensive disease in pregnancy, a systematic review. *Hypertension in Pregnancy* 29: 206–30

Abstract: www.informahealthcare.com/doi/abs/10.3109/10641950902968668?journalCode=hip

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Reducing the risk of hypertensive disorders in pregnancy

- How early in pregnancy to start taking aspirin for women at moderate or high risk of pre-eclampsia to reduce the incidence of pre-eclampsia, intrauterine growth restriction and pre-term birth
www.library.nhs.uk/DUETs/viewResource.aspx?resid=411895
- Serious adverse infant and long-term childhood outcomes with using anti-clotting medications during pregnancy
www.library.nhs.uk/DUETs/viewResource.aspx?resid=412266

Medical management of severe hypertension or severe pre-eclampsia in a critical care setting

- Corticosteroids for HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome in pregnancy
www.library.nhs.uk/duets/ViewResource.aspx?resID=405248

Further evidence uncertainties can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Hypertension in pregnancy. NICE clinical guideline 107 (2010). Available from www.nice.org.uk/guidance/CG107

Searches

The literature was searched to identify RCTs and reviews about the management of hypertensive disorders during pregnancy, relevant to the scope. Searches were conducted of the following databases, covering the dates 20 May 2009 (the end of the search period for the reference guidance) to 14 December 2011:

- MEDLINE
- EMBASE
- Three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects)
- NHS Economic Evaluation Database
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

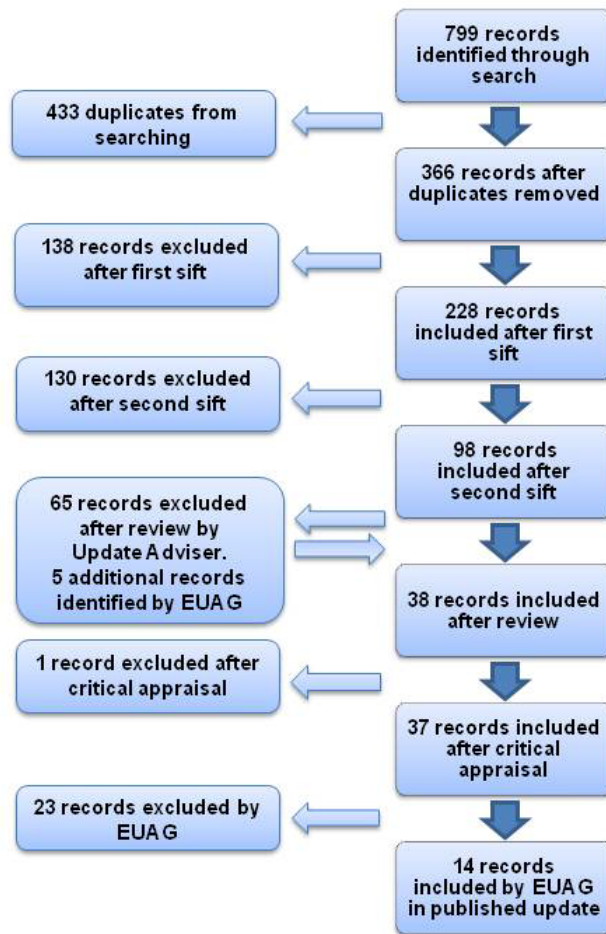
Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. A highly specific search strategy was developed to provide a focused set of results, which was thoroughly tested to ensure that the comprehensiveness of the results was not compromised. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Hypertension, Pregnancy-Induced/	6	Preeclamp\$.tw
2	Pregnancy/ and Hypertension/	7	Pre?eclamp\$.tw
3	Pre-Eclampsia/	8	Eclampsia/
4	HELLP Syndrome/	9	HELLP.tw.
5	((pregnan\$ or gestation\$) adj3 hypertensi\$).tw	10	(prehypertensi\$ and pregnan\$).tw
		11	or/1-10

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group



Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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