6-year surveillance (2017)

Hypertension in pregnancy: diagnosis and management (2010)
NICE guideline CG107

Appendix A: Summary of new evidence from surveillance

Reducing the risk of hypertensive disorders in pregnancy

107-01 **What interventions (including lifestyle advice) are effective at reducing the incidence of hypertensive disorders in pregnancy?**

Recommendations derived from this question

1.1.1 Symptoms of pre-eclampsia

1.1.1.1 Pregnant women should be made aware of the need to seek immediate advice from a healthcare professional if they experience symptoms of pre-eclampsia. Symptoms include:

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe pain just below the ribs
- vomiting
- sudden swelling of the face, hands or feet.

[This recommendation is adapted from 'Antenatal care' (NICE clinical guideline 62)].

1.1.2 Antiplatelet agents

1.1.2.1 Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

1.1.2.2 Advise women with more than one moderate risk factor for pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Factors indicating moderate risk are:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m^2 or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.

1.1.3 Other pharmaceutical agents

1.1.3.1 Do not use the following to prevent hypertensive disorders during pregnancy:

*In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

- nitric oxide donors
- progesterone
- diuretics
- low molecular weight heparin

1.1.4 Nutritional supplements

1.1.4.1 Do not recommend the following supplements solely with the aim of preventing hypertensive disorders during pregnancy:

- magnesium
- folic acid
- antioxidants (vitamins C and E)
- fish oils or algal oils
- garlic.

1.1.5 Diet

1.1.5.1 Do not recommend salt restriction during pregnancy solely to prevent gestational hypertension or pre-eclampsia.

1.1.6 Lifestyle

1.1.6.1 Advice on rest, exercise and work for women at risk of hypertensive disorders during pregnancy should be the same as for healthy pregnant women (see 'Antenatal care', NICE clinical guideline 62).

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

L-arginine

Two RCTs[1,2] were identified that investigated the effect of L-arginine during pregnancy. In the first study[1], women with mild chronic hypertension (n=80) were randomised to L-arginine or placebo. No difference between groups was found for blood pressure change. The second RCT[2] randomised women at high risk of pre-eclampsia (n=672) to food bars containing L –arginine and antioxidants, food bars with antioxidants only or to placebo bars. Results showed that L-arginine and antioxidant vitamins did significantly reduce pre-eclampsia or eclampsia when compared to the control.

The Evidence Update concluded that further research would be required before such supplements could be considered for inclusion in the guideline.

Heparin

A Cochrane review[3] looking at heparin in women at risk of placental dysfunction was also identified. This included five RCTs (n=484) comparing heparin with no treatment or trapidil (triazolopyrimidine, not licensed in the UK) to placebo. The primary outcomes of interest (perinatal mortality, preterm birth at less than 34 weeks of gestation and major neurodevelopmental handicap at childhood follow up) were not reported in the trapidil study. For those studies involving heparin, no statistically significant difference for any of the primary outcomes was found. However, heparin was found to be associated with a reduction in pre-eclampsia, eclampsia and infant birthweight less than the 10th centile for gestational age.

For heparin, the Evidence Update suggested that the evidence identified was consistent with current recommendations not to use this drug. The Evidence Update also suggested that further RCTs of sufficient size are needed to examine adverse outcomes for infants and long-term childhood outcomes.

Nutritional supplements

A meta-analysis[4] of 9 RCTs (n=19675) found that vitamin C and E supplementation was ineffective in preventing hypertensive disorders

during pregnancy. It was suggested that they may be harmful leading to an increased risk of gestational hypertension.

The Evidence Update concluded that the evidence for nutritional supplements was consistent with CG107 which advises that antioxidants and other nutritional supplements are not recommended solely with the aim of preventing hypertensive disorders during pregnancy.

Prediction tests

A systematic review[5] assessed the efficacy of 24 prediction tests in women with a history of hypertensive disorders during a previous pregnancy. The authors found few single factors to predict the risk of recurrent hypertensive disease in pregnancy with both high sensitivity and specificity. Furthermore, only three tests showed reasonable predictive capacity with both sensitivity and specificity higher than 50% (low plasma volume, high resistance index and the presence of early diastolic notch in the uterine arteries at 24 weeks gestation and a multivariable model including longitudinal in-pregnancy patterns).

4-year surveillance summary
Nitric Oxide agents/donors/precursors
Donors

An RCT[6] investigated the effectiveness of Nitric oxide (NO)-donors like pentaerithrityl-tetranitrate (PETN) for the secondary prevention of intrauterine growth restriction (IGUR), pre-eclampsia and pre-term birth. One hundred and eleven women with abnormal placental perfusion at 19-24 weeks gestation were randomised to NO-donors PETN or placebo. Results showed that NO-donors significantly decreased IGUR, perinatal death risk and pre-term birth before 32 weeks gestation.

Precursors

The effect of L-arginine supplementation on blood pressure in pregnancy was examined in a meta-analysis[7]. This included five trials. Results showed L-arginine to significantly lower diastolic blood pressure and prolong gestation age but no reduction in systolic blood pressure was found when compared to placebo.

A systematic review[8] also investigated the role of L-arginine in the prevention and treatment of pre-eclampsia. It included seven RCTs (n=884). The results indicated that L-arginine was associated with a reduction in pre-eclampsia and a reduction in the risk of preterm birth when compared to placebo. However, the authors concluded that further well-designed, adequately powered trials are needed.

Low molecular weight heparin (LMWH)
A multicentre RCT[9] was identified which randomised 139 pregnant women with inheritable thrombophilia and prior delivery for hypertensive disorders and/or small for gestational age infants to LMWH plus aspirin daily or to aspirin alone. It was found that LMWH plus aspirin reduced recurrent hypertensive disorder onset < 34 weeks duration.

Diet and lifestyle

A meta-analysis[10] was identified which looked at the effect of diet and lifestyle interventions based on metabolic risk modifying on the risk of pre-eclampsia. Eighteen studies (n=8712) were included with six studies examining diet, six studies looking at mixed interventions and six studies investigating essential fatty acid supplementation. Overall, the interventions reduced the risk of pre-eclampsia when compared to the controls. However, whilst dietary interventions reduced the risk of pre-eclampsia by 33%, mixed interventions and essential fatty acids showed no reduction in risk.

Physical Activity
The impact of physical activity before and during early pregnancy on the risk of pre-eclampsia was investigated in a meta-analysis[11]. Fifteen case-control and cohort studies were included. The results showed that physical activity before and during early pregnancy reduced the risk of pre-eclampsia.

A systematic review[12] also investigated the impact of exercise on the prevention of pre-eclampsia. This included 17 studies, 16 of which were observational and one RCT. Physical activity was found to have a protective effect in the six case-control studies and one RCT that were included. The 10 included prospective cohort studies found no significant difference.

Nutritional Supplements
N-3

A multicentre RCT[13] was identified which investigated whether n-3 long chain polyunsaturated fatty acids in pregnancy reduced gestational diabetes mellitus and pre-

eclampsia incidence. Women of <21 weeks gestation (n=2399) were randomised to either docosahexaenoic acid enriched fish oil or vegetable oil capsules from trial entry to birth. Overall, n-3 supplementation did not reduce the risk of pre-eclampsia or gestational diabetes. The authors suggested that further investigation is required into the risk of perinatal death and neonatal convulsions and n-3 supplementation.

Vitamin D

A meta-analysis[14] investigated the role of vitamin D in the development of pre-eclampsia. The results showed vitamin D supplementation reduced the risk of pre-eclampsia. It was suggested that low maternal serum 25-hydroxyvitamin D (25(OH)D) concentrations increase pre-eclampsia risk. The number of studies included in the meta-analysis was not reported.

The association between vitamin D and pre-eclampsia risk was also investigated in another meta-analysis[15]. This included 15 observational studies. A significant association was found between vitamin D deficiency and pre-eclampsia risk. However, whilst this association was significant for studies that defined vitamin D deficiency as 25(OH)D < 50nmol/L it was not significant for those that considered vitamin D deficiency as< 38nmol/l. Significant between-study heterogeneity was also identified.

Tocotrienol-rich fraction

An RCT[16] was identified which investigated the role of tocotrienol-rich fraction (TRF) of palm oil in preventing hypertension in pregnancy. Two hundred and ninety nine women were randomised to the TRF arm or placebo. Overall, the results indicated that TRF did not significantly reduce the risk of developing hypertension in pregnancy.

Vitamin C

An RCT[17] randomised pregnant women with gestational ages between 12 to 22 weeks (n=932) to vitamin C or placebo daily until they delivered. No difference in the incidence of pre-eclampsia, severe pre-eclampsia, gestational hypertension, pre-term delivery, low birth weight and still birth delivery was found between the two groups.

Magnesium

An RCT[18] examined magnesium supplementation to prevent high blood pressure in pregnancy. Women were randomised to magnesium or placebo. It was found that the number of women with an increase in diastolic blood pressure of > 15 mmHG was significantly lower in the magnesium group. An inverse relationship between the urinary excretion of magnesium during pregnancy and diastolic blood pressure was also found.

Phytonutrient supplementation

An RCT[19] randomised 684 women to a supplement of blended fruit and vegetable juice power concentrate or placebo in the first trimester of pregnancy. Only 267 participants completed the study. Overall, results showed that the intervention did not decrease pre-eclampsia rates. However, nonsignificant trends towards lower placenta-related obstetrical complications were found along with decreased rates of respiratory distress syndrome in infants born to the supplemented mothers at high risk of pre-eclampsia.

Antioxidants

The efficacy of antioxidants for the prevention of pre-eclampsia was investigated in a systematic review[20]. Fifteen RCTs were included. No statistically significant difference was found between antioxidant and placebo groups for pre-eclampsia, severe pre-eclampsia, preterm birth and gestational age size. Side effects were found to be more frequent in the antioxidant group than in the placebo group. However, this difference was not statistically significant.

Overall, the new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

6-year surveillance summary

Low molecular weight heparin

A systematic review[21] (4 trials, n=222) found no evidence of incremental benefit of adding LMWH to aspirin in pregnant women with hereditary thrombophilia, in terms of reduction of risk of pre-eclampsia among other outcomes.

Diet and lifestyle

Physical activity

A systematic review[22] (65 studies,11 studies covering hypertension n=5162) of diet or exercise, or both, for preventing excessive weight gain in pregnancy found that maternal hypertension (not a pre-specified outcome) was

reduced in the intervention group compared with the control group overall.

Nutritional supplements

Calcium

A systematic review[23] (4 studies, n=unreported in abstract) found that calcium supplementation during pregnancy reduced the risk of hypertension in the calcium group. However, there was no reduction in the risk of severe gestational hypertension, pre-eclampsia, severe pre-eclampsia, preterm birth and low birthweight.

A further systematic review[24] found that calcium supplementation in pregnancy reduced the overall risk of pre-eclampsia in 10 trials (n = 24 787). However, potential publication bias and a lack of large trials limited the impact of the results.

Vitamin D

Three systematic reviews[25-27] assessed the effects of vitamin D supplementation during pregnancy. The first review[25] (7 studies) found conflicting results about the association between vitamin D levels and the risk of preeclampsia. However, more than half of the studies showed a positive link between vitamin D deficiencies and pre-eclampsia. It should be noted that only one of the included studies was an RCT. An update of a Cochrane review[26] (15 trials n=2833 women) found that data from two trials (n=219) suggested that women who received vitamin D supplements may have a lower risk of pre-eclampsia than those receiving no intervention or placebo, but further research was recommended to confirm the findings. A further review[27](13 studies, n=2299) found that incidence of pre-eclampsia was not influenced by vitamin D supplementation.

Vitamin B6

A Cochrane systematic review[28] (4 trials, n=1646) found that pyridoxine (vitamin B6) supplementation during pregnancy did not reduce the risk of eclampsia (capsules: 3 trials; n = 1242; lozenges: 1 trial; n = 944), or pre-eclampsia (capsules 2 trials; n = 1197; lozenges: 1 trial; n = 944).

Vitamin C

A Cochrane systematic review[29] (16 trials for preeclampsia, n=21,956) found no significant differences between women supplemented with vitamin C alone or in combination with other supplements compared with placebo or no control for the risk of pre-eclampsia.

Vitamin E

An update of a Cochrane systematic review[30] (21 trials, n=22,129) found that the collective data did not support routine vitamin E supplementation in pregnancy, in combination with other supplements, for the prevention of pre-eclampsia, amongst other adverse outcomes.

Folic acid

A systematic review[31] (6 studies, n=201,661) found that multivitamins containing folic acid or folic acid alone were not significantly effective in reducing gestational hypertension or pre-eclampsia incidence during pregnancy.

Fish Oil

A systematic review[32] (11 trials, n>5000) found that fish oil supplementation during the second or third trimester of pregnancy did not reduce the risk of pregnancy induced hypertension or pre-eclampsia.

Antenatal care programmes

An updated Cochrane systematic review[33] (6 studies, n=54,108 women) found that antenatal care programmes with reduced visits for low-risk women did not significantly affect hypertensive disorders of pregnancy (various definitions including pre-eclampsia) when compared with standard care. However, the evidence was graded as low quality and caution was advised in interpretation due to varying definitions of pre-eclampsia between trials.

Interventions for obesity

A systematic review[34] (11 studies) of cohort studies found that bariatric surgery in obese women prior to pregnancy significantly reduced the risk of hypertensive disorders during pregnancy. However, their odds of small-for-gestational-age newborns were increased.

A further systematic review[35] found no RCTs that assessed the effect of preconception health programmes and interventions, including bariatric surgery, in overweight and obese women with the aim of improving pregnancy outcomes.

Pharmacological interventions

An RCT[36] (n=400) found among women without diabetes who had a body mass index of more than 35, the antenatal administration of

metformin reduced the incidence of preeclampsia, a secondary outcome in the study. The primary outcome of reduction in the median neonatal birth-weight was non-significant.

Topic expert feedback
An RCT[36] was highlighted relating to metformin in women without diabetes, and is included in the evidence summary. No comments were made regarding this intervention.

Topic expert feedback highlighted that metformin is not licensed for pregnancy without diabetes.

Impact statement
Low molecular weight heparin

The new evidence on LMWH is consistent with recommendation 1.1.3.1 which advises against its use in pregnancy.

Physical activity

The new evidence on physical activity is consistent with the cross referred recommendation 1.3.7.1 in the Antenatal care NICE guideline CG62, which states that pregnant women should be informed that beginning or continuing a moderate course of exercise during pregnancy is not associated with adverse outcomes.

Nutritional supplements

The new evidence on the following nutritional supplements is consistent with recommendation 1.1.4.1 advising against recommending their use in pregnancy solely with the aim of preventing hypertensive disorders:

- folic acid
- antioxidants (vitamins C and E)
- fish oils

The new evidence on the effect of vitamin D and calcium in reducing the risk of hypertension is inconclusive and further, more robust research may be needed to establish an impact on the guideline. The new evidence on vitamin B6 does not support its use in pregnancy to reduce the risk of hypertension.

Antenatal care programmes

The new evidence on the use of antenatal care programmes with reduced visits for low-risk women to reduce the risk of hypertensive disorders in pregnancy is based on low quality, heterogeneous trials in varying country settings and is therefore insufficient to have any impact on the guideline. Further research in high income settings may be needed in this area to establish an impact on the guideline.

Interventions for obesity

The most robust new systematic review evidence does not support health programmes and interventions for overweight and obese women solely to reduce the risk of hypertensive disorders. Further research may be needed on bariatric surgery in order to establish an impact on the guideline.

Pharmacological interventions

NICE guideline CG107 does not make any recommendations for metformin in pregnancy, and metformin is not licensed for the indication of pregnancy without diabetes. New RCT evidence indicates that antenatal metformin in women without diabetes and with a body mass index greater than 35 may reduce the incidence of preeclampsia, but further RCT evidence may be needed to establish a definite impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Management of pregnancy with chronic hypertension

Women with chronic hypertension should be given advice and treatment in line with 'Hypertension: the management of hypertension in adults in primary care' (NICE clinical guideline 34) (replaced by 'Hypertension: clinical management of primary hypertension in adults' [NICE clinical guideline 127]), unless it specifically differs from recommendations in this guideline.

107-02 What advice/interventions should be offered to women with chronic hypertension planning to become pregnant?

Subquestion

What is the risk of congenital malformation/IUGR occurring in women taking ACEs or ARBs for chronic hypertension?

How frequently should blood pressure be measured in pregnant women with chronic hypertension?

What pre-pregnancy advice should be given to pregnant women with chronic hypertension?

Recommendations derived from this question

1.2.1 Pre-pregnancy advice

1.2.1.1 Tell women who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs):

- that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

1.2.1.2 Stop antihypertensive treatment in women taking ACE inhibitors or ARBs if they become pregnant (preferably within 2 working days of notification of pregnancy) and offer alternatives.

1.2.1.3 Tell women who take chlorothiazide:

- that there may be an increased risk of congenital abnormality and neonatal complications if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

1.2.1.4 Tell women who take antihypertensive treatments other than ACE inhibitors, ARBs or chlorothiazide that the limited evidence available has not shown an increased risk of congenital malformation with such treatments.

1.2.2 Diet

1.2.2.1 Encourage women with chronic hypertension to keep their dietary sodium intake low, either by reducing or substituting sodium salt, because this can reduce blood pressure. (This recommendation is adapted from 'Hypertension: management of hypertension in adults in primary care' [NICE clinical guideline 34] [replaced by 'Hypertension: clinical management of primary hypertension in adults NICE clinical guideline 127].)

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
A meta-analysis[37] was identified that investigated chronic hypertension and pregnancy outcomes. Fifty five studies were included. The authors found that women with chronic hypertension had high incidences of superimposed pre-eclampsia, caesarean section, pre-term delivery < 37 weeks gestation, birth weight <2500g, neonatal unit admission and perinatal death. However, considerable heterogeneity existed between the included studies.

Education Tool
An RCT[38] assessed if exposure to a standardised education tool to inform women about pre-eclampsia led to a better

understanding of the syndrome. Women (n=120) were randomised to the standardised education tool, a standard pamphlet or no additional information. It was found that women in the standardised education tool group scored significantly higher on the pre-eclampsia questionnaire compared to those in the other groups.

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations. No new evidence was identified at the 6-year surveillance that would change those conclusions.

The initiation of ACEI and ARB in women of childbearing age is covered in Hypertension: clinical management of primary hypertension in adults NICE clinical guideline 127.

New evidence is unlikely to change guideline recommendations.

107-03 What interventions for chronic hypertension are effective at improving outcomes for women and infants?

Recommendations derived from this question

1.2.3 Treatment of hypertension

1.2.3.1 In pregnant women with uncomplicated chronic hypertension aim to keep blood pressure lower than 150/100 mmHg.

1.2.3.2 Do not offer pregnant women with uncomplicated chronic hypertension treatment to lower diastolic blood pressure below 80 mmHg.

1.2.3.3 Offer pregnant women with target-organ damage secondary to chronic hypertension (for example, kidney disease) treatment with the aim of keeping blood pressure lower than 140/90 mmHg.

1.2.3.4 Offer pregnant women with secondary chronic hypertension referral to a specialist in hypertensive disorders.

1.2.3.5 Offer women with chronic hypertension antihypertensive treatment dependent on pre-existing treatment, side-effect profiles and teratogenicity.

1.2.4 Antenatal consultations

1.2.4.1 In women with chronic hypertension, schedule additional antenatal consultations based on the individual needs of the woman and her baby.

1.2.5 Timing of birth

1.2.5.1 Do not offer birth to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, before 37 weeks.

1.2.5.2 For women with chronic hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

1.2.5.3 Offer birth to women with refractory severe chronic hypertension, after a course of corticosteroids (if required) has been completed.

1.2.6 Postnatal investigation, monitoring and treatment

1.2.6.1 In women with chronic hypertension who have given birth, measure blood pressure:

- daily for the first 2 days after birth
- at least once between day 3 and day 5 after birth

- as clinically indicated if antihypertensive treatment is changed after birth.

1.2.6.2 In women with chronic hypertension who have given birth, aim to keep blood pressure lower than 140/90 mmHg.

1.2.6.3 In women with chronic hypertension who have given birth:

- continue antenatal antihypertensive treatment.
- review long-term antihypertensive treatment 2 weeks after the birth.

1.2.6.4 If a woman has taken methyldopa to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was taking before she planned the pregnancy.

1.2.6.5 Offer women with chronic hypertension a medical review at the postnatal review (6–8 weeks after the birth) with the pre-pregnancy care team.

Surveillance decision

This review question should be updated.

2-year Evidence Update summary

A systematic review[39] was identified that investigated nicardipine in women with severe chronic or gestational hypertension. Five studies (n=147) were included. All included studies showed a significant reduction in blood pressure with nicardipine and no maternal or fetal side effects were reported.

The Evidence Update stated that this evidence is unlikely to currently affect guidance. This is because the size and design of the included studies precluded detailed analysis of outcomes. More prospective RCTs were considered necessary in order to establish the efficacy and safety of nicardipine. Nicardipine is not currently recommended by the guideline.

4-year surveillance summary

Type of control

A multicentre RCT[73] was identified which aimed to determine the best management of hypertension in women with non-proteinuric pre-existing or gestational hypertension. Women (n=1030) were randomised to less tight or tight control. The findings suggested that women in the less tight control group had higher diastolic blood pressure and more frequently developed blood pressure of at least 160/110mmHg compared to the tight control group. However, similar rates of adverse perinatal outcomes and maternal outcomes were seen between the groups.

Recording Blood Pressure

An RCT[40] randomised 220 pregnant women with hypertension to have blood pressure recorded with mercury sphygmomanometry or an automated blood pressure device for the remainder of their pregnancy. Maternal and fetal outcomes were found to be similar between the two groups.

Drugs

A pilot RCT[41] looked at the efficacy and safety of furosemide, amlodipine or aspirin for the management of chronic hypertension in pregnancy. Sixty-three pregnant women with mild to moderate chronic hypertension were randomised to oral furosemide each day, oral amlodipine each day or oral acetylsalicylic acid (aspririn) each day. No difference was found between groups in maternal complications, pre-term birth, mean birth weight or in the proportion of small for gestational age infants. In addition, the rates of severe hypertension and pre-eclampsia were similar between groups.

An updated Cochrane review[42] investigated antihypertensive drug treatments for mild to moderate hypertension in pregnancy. Forty-nine trials were included with 29 comparing antihypertensives with placebo or no

*In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

antihypertensive and 22 trials comparing one antihypertensive with another. For the trials comparing antihypertensive with placebo or no antihypertensive the results showed the risk of developing severe hypertension to be halved with the intervention. However, there was little evidence found for a difference in the risk of pre-eclampsia, pre-term birth, small for gestational age babies or risk of neonatal death. For studies comparing antihypertensives, other drugs appeared to be more effective than methyldopa. For instance, beta-blockers and calcium channel blockers both led to a reduction in the overall risk of pre-eclampsia and proteinuria compared to methyldopa. Furthermore, this drug did not appear to reduce the risk of severe hypertension as well as other drugs. The authors concluded that it is unclear which antihypertensive drug for mild to moderate hypertension in pregnancy is best.

Another updated Cochrane review[43] compared different antihypertensive drugs for very high blood pressure during pregnancy in women with severe hypertension. It included 35 RCTs (n=3573) with 15 comparisons. It found that calcium channel blockers reduced persistently high blood pressure when compared to hydralazine. Furthermore, ketanserin (not licensed in the UK) versus hydralazine was associated with more persistent high blood pressure but had fewer adverse effects and a lower risk of haemolysis, elevated liver enzymes and lowered platelets (HELLP) syndrome. Labetalol, on the other hand, lowered hypotension risk and the risk of caesarean section when compared to diazoxide. Both nimodipine and magnesium sulphate were associated with a higher incidence of persistent high blood pressure. However, nimodipine reduced the risk of respiratory difficulties, had fewer adverse effects and had less postpartum haemorrhage compared to magnesium sulphate. The authors concluded that while antihypertensives are effective there is not enough evidence to suggest which is the most effective. Further research is needed.

A meta-analysis[44] assessed the efficacy of nifedipine and hydralazine in 50 pregnant women with hypertension. Women were randomised to either oral nifedipine or intravenous hydralazine. Results showed that nifedipine required a shorter amount of time to reduce blood pressure and less frequent doses were required compared to hydralazine, However, there was one episode of hypotension after nifedipine but no episodes after hydralazine.

The effectiveness of oral antihypertensives for the treatment of severe pregnancy/postpartum hypertension was also examined in a systematic review[45]. Fifteen RCTs were included. Nifedipine achieved treatment success in most of the included women as did hydralazine and labetalol. Furthermore less than 2% of those treated with nifedipine experienced hypotension. No difference was seen between antihypertensives in adverse maternal or fetal outcomes.

Exercise

The association between exercise and maternal and neonatal outcomes in women with chronic hypertension was evaluated in a RCT[46]. Women (n=116) were randomised to exercise with a stationary bike once a week for 30 minutes or to no exercise. The results indicated that there was no difference between groups in type of delivery, maternal morbidity, hospitalisation to the intensive care unit or neonatal morbidity.

Timing of delivery in those with chronic hypertension

An RCT[47] investigated elective delivery at 37 weeks and expectant management in pregnant women with mild to moderate chronic hypertension. Women (n=76) were randomised to planned delivery at 37 weeks or expectant management for spontaneous onset of labour or reaching 41 weeks. No difference was seen between groups for superimposed pre-eclampsia, severe hypertension, preterm delivery, placental abruption, oligohydramnios, intrauterine growth restriction or perinatal mortality. However, those in the expectant management group had higher gestational age at delivery and birth weight but lower caesarean and neonatal care unit admission rates.

6-year surveillance summary

No relevant evidence was identified

Topic expert feedback

The CHIPS study[73] was highlighted as a key study in this area, and is covered in the 4 year surveillance evidence summary. It was also highlighted in the stakeholder consultation for the 4-year surveillance, in the context of the target diastolic blood pressure for chronic

hypertension. The target blood pressure for pregnant women with target-organ damage secondary to chronic hypertension recommended in NICE CG107 (1.2.3.3) is 90 mmHG. This was proposed for review by the stakeholder in line with the intervention in the trial for tight control (85 mmHg). However, the trial did not report the inclusion criterion of women with target-organ damage.

Impact statement
The new evidence identified at the 4-year surveillance review on recording blood pressure, drugs, exercise and timing of delivery was considered unlikely to impact on guideline recommendations.

The new evidence from the full results of the CHIPS study may potentially impact on recommendations 1.2.3.1 and 1.2.3.2, on the basis of topic expert and clinical adviser feedback. These recommendations were informed by the CHIPS pilot study and advise aiming to keep blood pressure lower than 150/100 mmHg, and not offering treatment to lower diastolic blood pressure below 80 mmHg, in pregnant women with uncomplicated chronic hypertension. There is a further potential impact on the guideline to update the evidence review with the full results of the CHIPS study, to replace the pilot study results.

There is unlikely to be any impact on recommended target blood pressure for women with target organ damage (1.2.3.3) as this was not an inclusion criterion for women in the CHIPS trial.

New evidence identified that may change current recommendations.

Assessment of proteinuria in hypertensive disorders of pregnancy

107-04 **Measurement of proteinuria**

Recommendations derived from this area (no questions made in guideline)

1.3.1.1 Use an automated reagent-strip reading device or a spot urinary protein:creatinine ratio for estimating proteinuria in a secondary care setting.

1.3.1.2 If an automated reagent-strip reading device is used to detect proteinuria and a result of 1+ or more is obtained, use a spot urinary protein:creatinine ratio or 24-hour urine collection to quantify proteinuria.

1.3.1.3 Diagnose significant proteinuria if the urinary protein:creatinine ratio is greater than 30 mg/mmol or a validated 24-hour urine collection result shows greater than 300 mg protein.

1.3.1.4 Where 24-hour urine collection is used to quantify proteinuria, there should be a recognised method of evaluating completeness of the sample.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
A systematic review[48] (7 studies, n=410) found that a 12-hour urine collection had predictive value for proteinuria in pregnant women with suspected preeclampsia. The optimal cut off point based on the receiver operating characteristic curve was 150 mg of protein on 12-hour collection. However, it should be noted that overall sample size was not reported in the abstract.

Topic expert feedback
Topic expert feedback indicated that clinically there is no great difference between a 24 and 12 hour collection. Both will take a considerable period of time to get a result and have the

same deficiency of ensuring a complete collection and then waiting for a lab result. The new evidence did not include a comparison with protein:creatinine ratio, which is the practical clinical test.

Impact statement

The new systematic review evidence indicating the predictive value of a 12 hour urine collection for assessment of proteinuria has a potential impact on recommendation 1.3.1.3, which advises a 24 hour collection result showing greater than 300 mg protein, or a protein:creatinine ratio greater than 30 mg/mmol. However, topic expert feedback indicated that the evidence is not sufficient to impact on the recommendation, because the 12 hour urine collection is not used in clinical practice.

The ongoing DAPPA trial compares methods of quantifying proteinuria and was considered by topic experts to have potential impact on the guideline recommendations. This trial is due to complete and publish in 2017 and will be monitored by the NICE Surveillance team.

New evidence is unlikely to change guideline recommendations.

Management of pregnancy with gestational hypertension

107-05 **What investigations, monitoring and advice should take place when gestational hypertension is diagnosed?**

Subquestion

What kind of monitoring should take place and in what frequency when new hypertension is diagnosed?

What investigations should take place when new hypertension is diagnosed?

Recommendations derived from this question

1.4.1 Treatment of hypertension

1.4.1.1 In women with gestational hypertension full assessment should be carried out in a secondary care setting by a healthcare professional who is trained in the management of hypertensive disorders.

1.4.1.2 In women with gestational hypertension, take account of the following risk factors that require additional assessment and follow-up:

- nulliparity
- age 40 years or older
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- multiple pregnancy
- BMI of 35 kg/m^2 or more
- gestational age at presentation
- previous history of pre-eclampsia or gestational hypertension
- pre-existing vascular disease
- pre-existing kidney disease.

1.4.1.3 Offer women with gestational hypertension an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in Table 1.

Table 1 Management of pregnancy with gestational hypertension

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol† as first-line treatment to keep: diastolic blood pressure between 80–100 mmHg systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: diastolic blood pressure between 80–100 mmHg systolic blood pressure less than 150 mmHg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent-strip reading device or urinary protein:creatinine ratio	At each visit using automated reagent-strip reading device or urinary protein:creatinine ratio	Daily using automated reagent-strip reading device or urinary protein:creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: kidney function, electrolytes, full blood count, transaminases, bilirubin

1.4.1.4 Only offer women with gestational hypertension antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine†.

1.4.1.5 In women receiving outpatient care for severe gestational hypertension, after it has been effectively controlled in hospital, measure blood pressure and test urine twice weekly and carry out weekly blood tests.

1.4.1.6 In women with mild hypertension presenting before 32 weeks, or at high risk of pre-eclampsia (see 1.1.1.1), measure blood pressure and test urine twice weekly.

1.4.1.7 Do not offer bed rest in hospital as a treatment for gestational hypertension.

Surveillance decision

This review question should be updated.

2-year Evidence Update summary

A systematic review[49] was identified that assessed 71 different combinations of biochemical and ultrasonographic markers to predict pre-eclampsia risk in pregnant women. Thirty-seven studies were included. Most of the markers evaluated were identified during the second trimester on small populations of

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

women already identified as at high risk. In the low risk population, combining markers, in most cases, increased sensitivity and/or specificity when compared to single markers. The authors concluded that more studies in large populations are needed before such approaches can be used for screening purposes.

4-year surveillance summary
Polymorphisms
SERPINE1 Polymorphism

A meta-analysis[50] examined the association between SERPINE1 (PAI-1) 4G/5G insertion/deletion promotor polymorphism (rs 1799889) and pre-eclampsia. Eleven studies were included. The meta-analysis found that this polymorphism was significantly associated with pre-eclampsia.

Circulating interleukin-18 and interferon gamma

A meta-analysis[51] was identified which looked at the association between pre-eclampsia and circulating interleukin-18 (IL-18) and interferon gamma (IFN-gamma). Thirty-seven studies were included. Overall, results showed that circulating higher IFN gamma levels may be associated with pre-eclampsia.

HLA-G gene polymorphism

A meta-analysis[52] examined the association between the 14bp insertion/deletion polymorphism of the HLA-G gene and pre-eclampsia. Ten case-control studies were included. It was found that paternal and fetal 14bp insertion/deletion polymorphism of the HLA-gene may be associated with pre-eclampsia.

Growth factor polymorphisms

The accuracy of circulating placental growth factor (PIGF), vascular endothelial growth factor (VEGF), soluble fms-like tyrosine kinase-1 (sFLT1) and soluble endoglin (sENG) to predict pre-eclampsia was assessed in a meta-analysis[53]. Thirty four studies were included. PIGF and VEGF were found to be lower in women who developed pre-eclampsia whilst sFLT1 and sENG were higher. However, the test accuracies of the four biomarkers were too poor to predict pre-eclampsia.

Markers

Biomarkers

A secondary analysis[54] of an RCT investigated early pregnancy biomarkers in women at high risk of pre-eclampsia. It was found that patterns of serum biomarkers vary according to the high-risk group in which the women were placed (Type 1 diabetes, hypertension, multiple gestation, pre-eclampsia). The findings suggested that multiple pathogenic pathways may lead to pre-eclampsia.

A meta-analysis[55] aimed to review the performance of combined abnormal first and/or second trimester maternal serum markers for predicting pre-eclampsia, small for gestational age and stillbirth beyond 24 weeks gestation. The meta-analysis included 15 studies. The authors found that no identifiable combinations of serum markers performed well as screening tests for pre-eclampsia, small for gestational age and stillbirth beyond 24 weeks. They concluded that large cohort studies with standardised screening test parameters and outcomes are needed.

6-year surveillance summary
Biomarkers
The following NICE guidance was published during the 6 year surveillance review:

PlGF-based testing to help diagnose suspected pre-eclampsia (2016) NICE diagnostic guidance DG23.

A systematic review[56] (30 studies, n=65,538) found that abnormal maternal blood biomarkers in early pregnancy were significantly associated with preeclampsia. The biomarkers PAPP-A, PP13, sFlt-1, pentraxin and inhibin-A were significantly associated with any preeclampsia. The odds of early onset pre-eclampsia were significantly increased when the biomarkers PlGF, PAPP-A, PP13, soluble endoglin and inhibin-A were abnormal. Two biomarkers, soluble endoglin and inhibin-A were significantly associated with late onset preeclampsia.

A systematic review[57] (7 studies, n=439) found that serum calprotectin was significantly raised among women with pre-eclampsia during the third trimester, suggesting it may have predictive value as a surveillance marker during the pregnancy course of women at risk of developing preeclampsia.

A systematic review[58] (15 studies) found that the combination of pulsatility index and different biomarkers or mean arterial pressure exhibited a good predictive ability for early-onset pre-eclampsia, and poor predictive ability for late-onset pre-eclampsia.

A systematic review[59] found that the efficacy of multiple potential biomarkers for pre-eclampsia was inconsistent and comparisons were difficult because of heterogeneity between different studies. Further research was recommended to identify the predictive best predictive marker(s) can be identified in order to improve the management of women destined to develop preeclampsia.

A systematic review[60] found that the genetic biomarker MTHFR C677T genotype was associated with increased risk for preeclampsia, especially in Asians and Caucasians.

An observational study[61] (n=500) found that a ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor of 38 or lower had predictive value for the short-term absence of pre-eclampsia in women in whom the syndrome was suspected. It did not have predictive value for the presence of pre-eclampsia within 4 weeks, however.

Topic expert feedback
Topic expert feedback indicated the possible need to consider the threshold and speed of treatment for severe hypertension in light of the confidential enquiry into maternal deaths:

Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer—2006–08:

The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom

This report supports CG107 but also recommends early treatment at less than150-160mmHg if severe hypertension is likely.

Topic expert feedback indicated that placental growth factor (PIGF) is an area of clinical interest and is advocated as a diagnostic test. It was considered to be of value in risk stratifying and deciding timing of birth, and needs NICE guidance as to whether it should become more routine practice than it is. This testing is covered by PIGF-based testing to help diagnose suspected pre-eclampsia (2016) NICE diagnostic guidance DG23.

Topic experts further advised that the question should be updated to incorporate the CHIPS study results. Topic experts stated that the full results elucidated the protection from severe hypertension if blood pressure is lowered to a diastolic level of 85 mmHg, which has a potential impact on Table 1 Management of pregnancy with gestational hypertension.

Impact statement
Timing of treatment for severe hypertension

Topic experts advised that Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer—2006–08: The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom is unlikely to impact on the guideline recommendations. This is because the evidence was based on observational data and expert advice, rather than on clinical trials.

However, there is a potential impact on Table 1 Management of pregnancy with gestational hypertension, to incorporate the CHIPS study results. Specifically, the target diastolic blood pressure may need to be reviewed to protect against severe hypertension, in line with the intervention in the trial for tight control (85 mmHg).

Polymorphisms

An association was found between pre-eclampsia and each of the polymorphisms identified during the current and previous surveillance reviews. However the evidence for these associations tended to be limited by small studies, or the sample sizes of multiple studies were unreported in the abstract. Further studies investigating different polymorphisms and their interactions, in addition to ethnic variations, may be needed before they can be considered for inclusion in the guideline.

Biomarkers

In terms of the evidence on biomarkers, the new evidence was inconclusive as in one systematic review the efficacy of multiple potential biomarkers for pre-eclampsia was inconsistent and comparisons were difficult because of heterogeneity between different studies. Other systematic review evidence suggests that abnormal maternal blood biomarkers in early pregnancy may be associated with preeclampsia. Further research may be needed to identify the best predictive marker(s) in order to improve the management of women destined to develop preeclampsia.

As such, the collective new evidence is unlikely to impact on CG107.

The ongoing IMPROVED trial is examining novel metabolomic and proteomic biomarkers to detect pre-eclampsia. This trial was still recruiting at the time of the 6 year surveillance review, and will be monitored by the NICE Surveillance team.

PlGF-based testing to help diagnose suspected pre-eclampsia (2016) NICE diagnostic guidance DG23 is relevant to recommendation 1.4.1.3 and Table 1, in terms of blood testing for women with gestational hypertension and suspected pre-eclampsia. However, this guidance has been incorporated into the Hypertension in pregnancy NICE pathway and is unlikely to impact on the guideline recommendation.

New evidence identified that may change current recommendations.

107-06 What interventions are effective in improving outcomes for women and infants with gestational hypertension?

Recommendations derived from this question

The same recommendations as in review question 107-05 were derived from this question.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary
Treatment of Hypertension
A systematic review[39] was identified that investigated nicardipine in women with severe chronic or gestational hypertension. Five studies (n=147) were included. All included studies showed a significant reduction in blood pressure with nicardipine and no maternal or fetal side effects were reported.

The Evidence Update stated that this evidence is unlikely to impact on the guideline. This is because the size and design of the included studies precluded detailed analysis of outcomes. It was stated that more prospective RCTs are needed in order to establish the efficacy and safety of nicardipine. Nicardipine is not currently recommended by the guideline.

4-year surveillance summary
Magnesium Sulphate
An RCT[62] randomised 48 women with gestational hypertension or mild pre-eclampsia at 34 weeks gestation or greater to magnesium sulphate or placebo. A significant decrease in fetal umbilical artery and middle cerebral artery pulsatility index were found with magnesium sulphate.

Antihypertensives
Three RCTs assessed nifedipine. The first[63] assessed the efficacy of nifedipine compared with methyldopa for the management of moderate pregnancy induced hypertension. One hundred pregnant women with hypertension were randomised to methyldopa or nifedipine. Both drugs were found to reduce hypertension with similar fetal and maternal outcome benefits. The second study[64] randomised 60 pregnant women with a sustained increase in systolic blood pressure of 160mmHg and diastolic blood pressure of 110mmHg or higher to oral nifedipine with intravenous placebo injection or intravenous labetalol injection with a placebo tablet. It was found that nifedipine lowered blood pressure more quickly than labetalol during hypertensive emergencies in pregnancy. However, in another RCT[65] which investigated oral nifedipine and intravenous labetalol results

showed both drugs to be as effective as each other for controlling severe hypertension in pregnancy.

The role of antihypertensive treatment for mild to moderate pregnancy induced hypertension was investigated in an RCT[66] looking at labetalol. This randomised 150 women to labetalol or methyldopa plus standard care or to standard care alone. Antihypertensive treatment was associated with a lower rate of severe pregnancy induced hypertension, proteinuria, hospitalisation before term and delivery by caesarean section. Results from the multivariable logistic models showed antihypertensive treatment to be associated with a lower incidence of preterm birth, small for gestational age babies, admission to a neonatal unit and adverse perinatal events.

L-arginine

A meta-analysis[67] investigated L-arginine supplementation for improving hypertensive pregnancy outcomes in women with gestational hypertension. Seven RCTs were included (n=916). Overall, the results showed that L-arginine significantly reduced pre-eclampsia and eclampsia incidence when compared to placebo. Furthermore, the intervention was beneficial in lowering diastolic blood pressure and prolonging pregnancy in those with gestational hypertension with or without proteinuria. However, L-arginine was found to not significantly reduce systolic blood pressure and the impact of this intervention on neonatal weight was unclear.

Nocturnal airflow limitation

An RCT[68] investigated if the application of treatment for sleep disordered breathing could improve blood pressure in women with gestational hypertension. Twenty four women were randomised to auto-titrating continuous positive airway pressure (auto-CPAP) or mandibular advancement device (MAD) plus a nasal strip. No improvement in blood pressure or inflammatory markers was found for either treatment.

6-year surveillance summary

Antihypertensives

A systematic review[69] (7 trials, n=363) found that oral nifedipine was associated with less risk of persistent hypertension and reported maternal side effects than labetalol for severe hypertension during pregnancy. However, on sensitivity analysis the outcome 'persistent hypertension' was no longer significant.

Dietary interventions

A systematic review[70] (28 RCTs) investigated the effect of dietary interventions before or during pregnancy on pregnancy outcomes. Dietary counselling during pregnancy was found to be effective in reducing systolic and diastolic blood pressure. Further high-quality RCTs, investigating micronutrient provision from food, and combination dietary intervention were recommended.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Antihypertensives

NICE guideline CG107 recommends treating with labetalol as first line treatment (1.4.1.4) and only offering women with gestational hypertension antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. It states that alternatives include methyldopa and nifedipine (1.4.1.4). The new evidence is generally supportive of these recommendations and therefore is unlikely to impact on the guideline at this time.

Other

The new evidence identified at the 4-year surveillance review on L-arginine and nocturnal airflow limitation was considered unlikely to impact on guideline recommendations.

The new evidence on dietary counselling during pregnancy to reduce systolic and diastolic blood pressure may require further research to confirm the findings.

New evidence is unlikely to change guideline recommendations.

107-07 What are the indications for timing, place and mode of birth in women with gestational hypertension?

Subquestion

What are the indications for timing of birth in women with a) gestational hypertension and b) pre-eclampsia?

Is there a difference in outcomes for babies of normal birthweight compared to small for gestational age in women with hypertension in pregnancy?

Recommendations derived from this question

1.4.2 Timing of birth

1.4.2.1 Do not offer birth before 37 weeks to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment.

1.4.2.2 For women with gestational hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

1.4.2.3 Offer birth to women with refractory severe gestational hypertension after a course of corticosteroids (if required) has been completed.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

An economic analysis[71] of a Dutch RCT (Hypertension and Pre-eclampsia Intervention Trial at Term (HYPITAT)) was identified. The clinical analysis[72] of this trial compared outcomes after induction of labour and expectant monitoring in pregnant women (n=756) with gestational hypertension or mild pre-eclampsia. Results showed that induction of labour after 37 weeks reduced the risk of poor maternal outcomes compared to expectant monitoring and found no difference in the rate of caesarean section between the two groups. The economic results showed that induction after 37 weeks was less costly than expectant monitoring. This was mainly because of reduced costs during the antepartum period. However, the impact of a potential increased rate of caesarean section in patients undergoing induction of labour was not included in the analyses.

The evidence identified in the Evidence Update was considered to be supportive of current recommendations in CG107 which recommend not offering birth before 37 weeks to women with gestational hypertension. Furthermore, the economic analysis provided reassurance that induction after 37 weeks was not more costly than expectant monitoring, if the rate of caesarean section was not increased.

4-year surveillance summary

Cervical favourability

A post-hoc analysis[74] of the HYPITAT trial examined if cervical favourability should inform decisions about labour induction. Women (n=756) were randomised to labour induction or expectant management. Analysis showed that women with gestational hypertension or mild pre-eclampsia who have an unfavourable cervix benefitted more from labour induction.

6-year surveillance summary

No relevant evidence was identified

Topic expert feedback

No topic expert feedback was relevant to this evidence.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

Impact statement

Overall, the new evidence identified from previous surveillance reviews was considered unlikely to impact on guideline recommendations.

For cervical favourability, the new evidence suggests that labour induction was most beneficial for women with gestational hypertension and an unfavourable cervix. Currently, CG107 does not make recommendations specific to cervical favourability. However, the new evidence was limited to a post-hoc analysis and so more research was considered necessary before considering cervical favourability in the guideline.

No new evidence was identified through the 6-year surveillance that would change these conclusions.

New evidence is unlikely to change guideline recommendations.

107-08 **What investigations, monitoring and advice should be given to women with hypertensive disorders of pregnancy, especially for those who wish to breastfeed, following discharge from critical care level 2/3?**

1.4.3 Postnatal investigation, monitoring and treatment

1.4.3.1 In women with gestational hypertension who have given birth, measure blood pressure:

- daily for the first 2 days after birth
- at least once between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

1.4.3.2 In women with gestational hypertension who have given birth:

- continue use of antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

1.4.3.3 If a woman has taken methyldopa† to treat gestational hypertension, stop within 2 days of birth.

1.4.3.4 For women with gestational hypertension who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if their blood pressure is higher than 149/99 mmHg.

1.4.3.5 Write a care plan for women with gestational hypertension who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed
- frequency of blood pressure monitoring needed
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review.

1.4.3.6 Offer women who have had gestational hypertension and remain on antihypertensive treatment 2 weeks after transfer to community care, a medical review.

1.4.3.7 Offer women who have had gestational hypertension a medical review at the postnatal review (6–8 weeks after the birth).

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

1.4.3.8 Offer women who have had gestational hypertension and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

Surveillance decision

No new information was identified at any surveillance review.

Management of pregnancy with pre-eclampsia

107-09 **What advice, investigations and monitoring should take place when pre-eclampsia is diagnosed?**

Recommendations derived from this question

1.5.1 Treatment of hypertension

1.5.1.1 Assess women with pre-eclampsia at each consultation. Assessment should be performed by a healthcare professional trained in the management of hypertensive disorders of pregnancy.

1.5.1.2 Offer women with pre-eclampsia an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in Table 2.

Table 2 Management of pregnancy with pre-eclampsia

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol† as first-line treatment to keep: diastolic blood pressure between 80–100 mmHg systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: diastolic blood pressure between 80–100 mmHg systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

1.5.1.3 Only offer women with pre-eclampsia antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine†.

Surveillance decision

This review question should be updated.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
Urgency of treatment

Topic experts advised that Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer—2006–08: The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom is unlikely to impact on Table 2 Management of pregnancy with pre-eclampsia, particularly as Table 2 already states that treatment should be carried out if blood pressure rises above 150 mmHg. Additionally, the report was based on observational data and expert advice, rather than on clinical trials. This report states that if the systolic pressure is very high, above 180 mmHg, this is a medical emergency that requires urgent as well as effective antihypertensive treatment.

It was noted in the 4 year surveillance review that CG107 did not make recommendations for nicardipine and MHRA alerted NICE that this drug is now licensed for the indication "Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated". Topic expert feedback indicated that nicardipine is now licensed for the indication of severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated.

Impact statement
Topic expert feedback indicated that the confidential enquiry into maternal deaths is unlikely to impact on Table 2 Management of pregnancy with pre-eclampsia. The recommendations in the confidential enquiry were based on reported cases and expert opinion, and no further evidence was identified to indicate an impact on CG107 at any surveillance review.

However, topic expert feedback indicated that nicardipine is now licensed for the indication of severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated. No systematic review evidence was identified at the 6 year review, but there is nevertheless a potential impact on Table 2, to consider nicardipine as an additional alternative licensed drug for severe pre-eclampsia.

New evidence identified that may change current recommendations.

107-10 What interventions are effective in improving outcomes for women and infants in women with pre-eclampsia?

Recommendations derived from this question

The same recommendations as in review question 107-09 were derived from this question.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

Surveillance decision

This review question should be updated.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
Abdominal decompression
An updated Cochrane review[75] examined the effects of antenatal abdominal decompression on perinatal outcomes. Three studies looking at this intervention in pre-eclampsia or suspected fetal compromise were included. Results showed therapeutic abdominal decompression to reduce persistent pre-eclampsia, fetal distress in labour, low birth weight, Apgar score less than six at one minute and perinatal mortality. However, the authors suggested that due to methodological limitations with the included studies, the effects of the interventions are unclear.

6-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
It was noted in the 4 year surveillance review that CG107 did not make recommendations for nicardipine and MHRA alerted NICE that this drug is now licensed for the indication "Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated". Topic expert feedback indicated that nicardipine is now licensed for the indication of severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated.

Impact statement
Overall, the new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

However, topic expert feedback indicated that nicardipine is now licensed for the indication of severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated. No systematic review evidence was identified at the 6 year review, but there is nevertheless a potential impact on recommendation 1.5.1.3, to consider nicardipine as an additional alternative licensed drug for severe pre-eclampsia.

New evidence identified that may change current recommendations.

107-11 What are the indications for timing of birth in women with pre-eclampsia?

Subquestion

What are the indications for timing of birth in women with a) gestational hypertension and b) pre-eclampsia?

Recommendations derived from this question

1.5.2 Timing of birth

1.5.2.1 Manage pregnancy in women with pre-eclampsia conservatively (that is, do not plan same-day delivery of the baby) until 34 weeks.

1.5.2.2 Consultant obstetric staff should document in the woman's notes the maternal (biochemical, haematological and clinical) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

1.5.2.3 Consultant obstetric staff should write a plan for antenatal fetal monitoring during birth.

1.5.2.4 Offer birth to women with pre-eclampsia before 34 weeks, after discussion with neonatal and anaesthetic teams and a course of corticosteroids has been given if:

- severe hypertension develops refractory to treatment
- maternal or fetal indications develop as specified in the consultant plan (see 1.5.22).

1.5.2.5 Recommend birth for women who have pre-eclampsia with severe hypertension after 34 weeks when their blood pressure has been controlled and a course of corticosteroids has been completed (if appropriate).

1.5.2.6 Offer birth to women who have pre-eclampsia with mild or moderate hypertension at 34+0 to 36+6 weeks depending on maternal and fetal condition, risk factors and availability of neonatal intensive care.

1.5.2.7 Recommend birth within 24–48 hours for women who have pre-eclampsia with mild or moderate hypertension after 37+0 weeks.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

An economic analysis[71] of a Dutch RCT (Hypertension and Pre-eclampsia Intervention Trial at Term (HYPITAT)) was identified. The clinical analysis[72] of this trial compared outcomes after induction of labour and expectant monitoring in pregnant women (n=756) with gestational hypertension or mild pre-eclampsia. Results showed that induction of labour after 37 weeks reduced the risk of poor maternal outcomes compared to expectant monitoring and found no difference in the rate of caesarean section between the two groups. The economic results showed that induction after 37 weeks was less costly than expectant monitoring. This was mainly because of reduced costs during the antepartum period. However, the impact of a potential increased rate of caesarean section in patients undergoing induction of labour was not included in the analyses.

A systematic review[76] looking at expectant management in women with severe pre-eclampsia was also identified. This included 72 observational studies and RCTs comparing outcomes associated with expectant and interventionist care. Results showed that expectant care was associated with greater pregnancy prolongation and that the neonatal death rate was higher with interventionist care. There was no difference between the two groups in rates of stillbirth.

The identified evidence from the Evidence update is supportive of the recommendation in CG107 to maintain pregnancy in women with pre-eclampsia conservatively until 34 weeks of gestation when possible. Furthermore, the economic analysis provides reassurance that induction after 37 weeks is not more costly than expectant monitoring, if the rate of caesarean section is not increased.

4-year surveillance summary

Route of delivery for eclampsia

An RCT[77] investigated the route of delivery in women with eclampsia. Two hundred women were randomised to caesarean or vaginal birth. Overall, maternal event rate was similar between groups and whilst neonatal event rates were less in the caesarean group the difference was not statistically significant.

Cervical favourability

A post-hoc analysis[74] of the HYPITAT trial examined if cervical favourability should inform decisions about labour induction. Women (n=756) were randomised to labour induction or expectant management. Analysis showed that women with gestational hypertension or mild pre-eclampsia who have an unfavourable cervix benefitted more from labour induction.

6-year surveillance summary

No relevant evidence was identified

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence identified at previous surveillance reviews was considered unlikely to impact on guideline recommendations. No new evidence was identified through the 6-year surveillance that would change those conclusions.

The ongoing PHOENIX trial is relevant to this question and research recommendation RR-04 and will be monitored by the NICE Surveillance team. The trial is addressing the uncertainty regarding the timing of delivery for pre-eclampsia between 34 to 37 weeks.

New evidence is unlikely to change guideline recommendations.

107-12 **What investigations, monitoring and treatment should be given to women with hypertensive disorders of pregnancy in the postnatal period, especially those discharged from critical care level 2/3? (question also relevant to Management of pregnancy with gestational hypertension)**

1.5.3 Postnatal investigation, monitoring and treatment (including after discharge from critical care)

Blood pressure

1.5.3.1 In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- at least once between day 3 and day 5 after birth
- on alternate days until normal if blood pressure was abnormal on days 3–5.

1.5.3.2 In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if blood pressure is 150/100 mmHg or higher.

1.5.3.3 Ask women with pre-eclampsia who have given birth about severe headache and epigastric pain each time blood pressure is measured.

1.5.3.4 In women with pre-eclampsia who took antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- every 1–2 days for up to 2 weeks after transfer to community care until the woman is off treatment and has no hypertension.

1.5.3.5 For women with pre-eclampsia who have taken antihypertensive treatment and have given birth:

- continue antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

1.5.3.6 If a woman has taken methyldopa† to treat pre-eclampsia, stop within 2 days of birth.

1.5.3.7 Offer women with pre-eclampsia who have given birth transfer to community care if all of the following criteria have been met:

- there are no symptoms of pre-eclampsia
- blood pressure, with or without treatment, is 149/99 mmHg or lower
- blood test results are stable or improving.

1.5.3.8 Write a care plan for women with pre-eclampsia who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed

- frequency of blood pressure monitoring
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review
- self-monitoring for symptoms.

1.5.3.9 Offer women who have pre-eclampsia and are still on antihypertensive treatment 2 weeks after transfer to community care a medical review.

1.5.3.10 Offer all women who have had pre-eclampsia a medical review at the postnatal review (6–8 weeks after the birth).

1.5.3.11 Offer women who have had pre-eclampsia and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

Haematological and biochemical monitoring

1.5.3.12 In women who have pre-eclampsia with mild or moderate hypertension, or after step-down from critical care:

- measure platelet count, transaminases and serum creatinine 48–72 hours after birth or step-down
- do not repeat platelet count, transaminases or serum creatinine measurements if results are normal at 48–72 hours.

1.5.3.13 If biochemical and haematological indices are improving but stay within the abnormal range in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated and at the postnatal review (6–8 weeks after the birth).

1.5.3.14 If biochemical and haematological indices are not improving relative to pregnancy ranges in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated.

1.5.3.15 In women with pre-eclampsia who have given birth, carry out a urinary reagent-strip test at the postnatal review (6–8 weeks after the birth).

1.5.3.16 In women with pre-eclampsia who have given birth and have stepped down from critical care level 2, do not measure fluid balance if creatinine is within the normal range.

1.5.3.17 Offer women who had pre-eclampsia and still have proteinuria (1+ or more) at the postnatal review (6–8 weeks after the birth) a further review at 3 months after the birth to assess kidney function and consider offering them a referral for specialist kidney assessment.

Surveillance decision

No new information was identified at any surveillance review.

Fetal monitoring

107-13 **What fetal assessments should occur in chronic hypertension, gestational hypertension or pre-eclampsia?**

Recommendations derived from this question

1.6.1 Chronic hypertension

1.6.1.1 In women with chronic hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery doppler velocimetry between 28 and 30 weeks and between 32 and 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

1.6.1.2 In women with chronic hypertension, only carry out cardiotocography if fetal activity is abnormal.

1.6.2 Mild or moderate gestational hypertension

1.6.2.1 In women with mild or moderate gestational hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery doppler velocimetry if diagnosis is confirmed at less than 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

1.6.2.2 In women with mild or moderate gestational hypertension, do not carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery doppler velocimetry if diagnosis is confirmed after 34 weeks, unless otherwise clinically indicated.

1.6.2.3 In women with mild or moderate gestational hypertension, only carry out cardiotocography if fetal activity is abnormal.

1.6.3 Severe gestational hypertension or pre-eclampsia

1.6.3.1 Carry out cardiotocography at diagnosis of severe gestational hypertension or pre-eclampsia.

1.6.3.2 If conservative management of severe gestational hypertension or pre-eclampsia is planned, carry out all the following tests at diagnosis:

- ultrasound fetal growth and amniotic fluid volume assessment
- umbilical artery doppler velocimetry.

1.6.3.3 If the results of all fetal monitoring are normal in women with severe gestational hypertension or pre-eclampsia, do not routinely repeat cardiotocography more than weekly.

1.6.3.4 In women with severe gestational hypertension or pre-eclampsia, repeat cardiotocography if any of the following occur:

- the woman reports a change in fetal movement
- vaginal bleeding
- abdominal pain
- deterioration in maternal condition.

1.6.3.5 In women with severe gestational hypertension or pre-eclampsia, do not routinely repeat ultrasound fetal growth and amniotic fluid volume assessment or umbilical artery doppler velocimetry more than every 2 weeks.

1.6.3.6 If the results of any fetal monitoring in women with severe gestational hypertension or pre-eclampsia are abnormal, tell a consultant obstetrician.

1.6.3.7 For women with severe gestational hypertension or pre-eclampsia, write a care plan that includes all of the following:

- the timing and nature of future fetal monitoring
- fetal indications for birth and if and when corticosteroids should be given
- when discussion with neonatal paediatricians and obstetric anaesthetists should take place and what decisions should be made.

1.6.4 Women at high risk of pre-eclampsia

1.6.4.1 Carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery doppler velocimetry starting at between 28 and 30 weeks (or at least 2 weeks before previous gestational age of onset if earlier than 28 weeks) and repeating 4 weeks later in women with previous:

- severe pre-eclampsia
- pre-eclampsia that needed birth before 34 weeks
- pre-eclampsia with a baby whose birth weight was less than the 10th centile
- intrauterine death
- placental abruption.

1.6.4.2 In women who are at high risk of pre-eclampsia (see 1.1.2.2), only carry out cardiotocography if fetal activity is abnormal.

Surveillance decision

No new information was identified at any surveillance review.

Intrapartum care

107-14 **What is the appropriate obstetric care of women with hypertensive disorders of pregnancy in the intrapartum period?**

Women with hypertensive disorders during pregnancy should be given advice and treatment in line with 'Intrapartum care: management and delivery of care to women in labour' (NICE clinical guideline 55), unless it specifically differs from recommendations in this guideline.

Recommendations derived from this question

1.7.1 Blood pressure

1.7.1.1 During labour, measure blood pressure:

- hourly in women with mild or moderate hypertension
- continually in women with severe hypertension.

1.7.1.2 Continue use of antenatal antihypertensive treatment during labour.

1.7.2 Haematological and biochemical monitoring

1.7.2.1 Determine the need for haematological and biochemical tests during labour in women with mild or moderate hypertension using the same criteria as in the antenatal period even if regional analgesia is being considered.

1.7.3 Care during epidural analgesia

1.7.3.1 Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia and combined spinal epidural analgesia.

1.7.4 Management of the second stage of labour

1.7.4.1 Do not routinely limit the duration of the second stage of labour:

- in women with stable mild or moderate hypertension **or**
- if blood pressure is controlled within target ranges in women with severe hypertension.

1.7.4.2 Recommend operative birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

An RCT[78] investigated outcomes in women with pre-eclampsia following intrapartum epidural analgesia compared to patient controlled analgesia with intravenous remifentanil (n=30). It was found that there were no significant differences in the level of analgesia or sedation level between groups.

Furthermore, there was no significant difference found between groups in nausea and vomiting and no significant difference in the neonates in Apgar score. However epidural analgesia was associated with more itching and hypotension.

A meta-analysis[79] was also identified. This found that epidural analgesia provided superior pain relief compared to remifentanil.

The Evidence Update concluded that the evidence was unlikely to impact on CG107. This was because an RCT with only 30 participants was too small to draw firm conclusions about the efficacy and safety of remifentanil. It was suggested that further research was needed into remifentanil as it may offer potential benefits in reducing hypertension risk.

4-year surveillance summary

Remifentanil

In an RCT[80], 75 women with severe pre-eclampsia were randomised to one of five remifentanil dose groups in order to determine which was the most effective dose. The effective dosage in 95% of the population for attenuating the hypertensive response to tracheal intubation during induction of anaesthesia for caesarean delivery was 1.34 μ/kg.

Another RCT[81] compared hemodynamic changes in pre-eclamptic women receiving remifentanil or fentanyl for caesarean section under general anaesthesia. A significant reduction in systolic blood pressure was found with remifentanil and a nonsignificant reduction in diastolic blood pressure. There was also a nonsignificant increase in heart rate with remifentanil. For fentanyl, a nonsignificant increase in systolic blood pressure and significant increases in diastolic blood pressure and heart rate were found.

6-year surveillance summary

No new evidence was identified that would affect recommendations.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence identified at previous surveillance reviews was considered unlikely to impact on guideline recommendations. No new evidence was identified through the 6-year surveillance that would change those conclusions.

New evidence is unlikely to change guideline recommendations.

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

107-15 **What is the appropriate medical management of women with severe pre-eclampsia or its complications in a critical care situation?**

Recommendations derived from this question

1.8.1 Anticonvulsants

1.8.1.1 If a woman in a critical care setting who has severe hypertension or severe pre-eclampsia has or previously had an eclamptic fit, give intravenous magnesium sulphate*.

1.8.1.2 Consider giving intravenous magnesium sulphate* to women with severe pre-eclampsia who are in a critical care setting if birth is planned within 24 hours.

1.8.1.3 If considering magnesium sulphate* treatment, use the following as features of severe pre-eclampsia:

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- severe hypertension and proteinuria **or**
- mild or moderate hypertension and proteinuria with one or more of the following:
  - symptoms of severe headache
  - problems with vision, such as blurring or flashing before the eyes
  - severe pain just below the ribs or vomiting
  - papilloedema
  - signs of clonus (≥3 beats)
  - liver tenderness
  - HELLP syndrome
  - platelet count falling to below 100 x 10^9 per litre
  - abnormal liver enzymes (ALT or AST rising to above 70 iu/litre).

1.8.1.4 Use the Collaborative Eclampsia Trial** regimen for administration of magnesium sulphate*:

- loading dose of 4 g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours
- recurrent seizures should be treated with a further dose of 2–4 g given over 5 minutes.

1.8.1.5 Do not use diazepam, phenytoin or lytic cocktail as an alternative to magnesium sulphate* in women with eclampsia.

1.8.2 Antihypertensives

1.8.2.1 Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with one of the following:

- labetalol† (oral or intravenous)
- hydralazine (intravenous)
- nifedipine† (oral).

1.8.2.2 In women with severe hypertension who are in critical care, monitor their response to treatment:

- to ensure that their blood pressure falls
- to identify adverse effects for both the woman and the fetus
- to modify treatment according to response.

1.8.2.3 Consider using up to 500 ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period.

1.8.2.4 In women with severe hypertension who are in critical care, aim to keep systolic blood pressure below 150 mmHg and diastolic blood pressure between 80 and 100 mmHg.

1.8.3 Corticosteroids for fetal lung maturation

1.8.3.1 If birth is considered likely within 7 days in women with pre-eclampsia:

- give two doses of betamethasone* 12 mg intramuscularly 24 hours apart in women between 24 and 34 weeks
- consider giving two doses of betamethasone* 12 mg intramuscularly 24 hours apart in women between 35 and 36 weeks.

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**The Eclampsia Trial Collaborative Group (1995) Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 345:1455–63

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1.8.4 Corticosteroids to manage HELLP syndrome

1.8.4.1 Do not use dexamethasone or betamethasone* for the treatment of HELLP syndrome.

1.8.5 Fluid balance and volume expansion

1.8.5.1 Do not use volume expansion in women with severe pre-eclampsia unless hydralazine is the antenatal antihypertensive.

1.8.5.2 In women with severe pre-eclampsia, limit maintenance fluids to 80 ml/hour unless there are other ongoing fluid losses (for example, haemorrhage).

1.8.6 Caesarean section versus induction of labour

1.8.6.1 Choose mode of birth for women with severe hypertension, severe pre-eclampsia or eclampsia according to the clinical circumstances and the woman's preference.

1.8.7 Indications for referral to critical care levels

1.8.7.1 Offer women with severe hypertension or severe pre-eclampsia referral to the appropriate critical care setting using the following criteria‡:

Level 3 care	Severe pre-eclampsia and needing ventilation
Level 2 care	Step-down from level 3 or severe pre-eclampsia with any of the following complications: – eclampsia – HELLP syndrome – haemorrhage – hyperkalaemia – severe oliguria – coagulation support – intravenous antihypertensive treatment – initial stabilisation of severe hypertension – evidence of cardiac failure – abnormal neurology
Level 1 care	– Pre-eclampsia with mild or moderate hypertension – Ongoing conservative antenatal management of severe preterm hypertension – Step-down treatment after the birth

‡ Table adapted by the Guideline Development Group from Intensive Care Society, Standards and Guidelines 2002

Surveillance decision

This review question should not be updated.

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2-year Evidence Update summary
Corticosteroids for HELLP syndrome
A Cochrane review[82] looked at the effects of corticosteroids on women with HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome who were pregnant. Eleven RCTs were included (n=550). These compared corticosteroids with placebo, no treatment, other drugs or alternative corticosteroids or corticosteroid dose regimen. Overall, there was no clear evidence of any effect of corticosteroids on substantive clinical outcomes. The authors concluded that there was insufficient evidence to support the use of steroids for the management of HELLP

The evidence identified in the Evidence Update was considered consistent with the current recommendation in CG107 not to use corticosteroids for HELLP syndrome.

4-year surveillance summary
Expectant management
To determine whether expectant management of severe pre-eclampsia prior to 34 weeks gestation was effective an RCT[83] was conducted. Women with severe hypertensive disorders (n=267) between 28 and 33 weeks gestation were randomised to steroids with prompt delivery after 48 hours or steroids and expectant management. No benefit on neonatal outcomes and perinatal mortality was found for expectant management. Furthermore, expectant management led to a risk of abruption and small for gestational age babies.

Prevention of postpartum haemorrhage.
An RCT[84] randomised women (n=60) with severe pre-eclampsia to receive oxytocin or carbetocin during the third stage of labour to prevent postpartum haemorrhage. The findings indicated that carbetocin was as effective as oxytocin in preventing postpartum haemorrhage and was not associated with oliguria or hypertension. Furthermore, the safety profiles were found to be similar between the two drugs.

Secondary prevention of placental vascular complications
A pilot RCT[85] was identified which investigated the addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. Two hundred and twenty four women were randomised to enoxaparin or no enoxaparin. The primary outcome was a composite of at least one of the following: pre-eclampsia, abruption placentae, birthweight < 5th percentile or fetal loss after 20 weeks. Results showed that enoxaparin was associated with a lower frequency of the primary outcome and had no obvious side effects.

Anti-digoxin antibody fragment antigen binding (DIF)
A secondary analysis[86] of the DEEP trial investigated if DIF treatment in women with severe pre-eclampsia was associated with positive endogenous digitalis like factors (EDLFs) in maternal serum improved outcomes. Analysis showed that women with positive EDLFs who received DIF had an attenuated decline in creatinine clearance from baseline compared to placebo. Furthermore, lower rates of pulmonary oedema and neonatal intraventricular haemorrhage were seen in the DIF group as was a lower use of antihypertensives. However, this did not reach statistical significance.

Labetalol
An RCT[87] randomised 200 women with severe pre-eclampsia to labetalol or hydralazine. No significant differences in systolic and diastolic blood pressure, time of delivery, Apgar score 1 minute, Apgar score 5 minute, caesarean section and abnormal bleeding after delivery were found between the two groups.

Type of care
A Cochrane review[88] investigated interventionist management versus expectant care for severe pre-eclampsia between 24 and 34 weeks gestation. Four trials randomising

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425 women were included. Results showed that women in the interventionist group were more likely to have a caesarean section. However, insufficient data was available for reliable conclusions about the comparative effects on the other outcomes for mothers. The babies of mothers assigned to the interventionist group had more interventricular haemorrhage and hyaline membrane disease, were more likely to have a lower gestation at birth and were more likely to be admitted to a neonatal intensive care unit. Furthermore, they required longer stays in ICU and required more ventilation. However, they were less likely to be small for gestational age. Insufficient data was available for reliable conclusions to be drawn about the effects of the interventions on stillbirth or death after delivery. The authors concluded that further larger trials are needed to confirm or refute the above findings and establish which approach is the safest.

Magnesium Sulphate

A systematic review[89] was conducted to investigate magnesium sulphate dosing regimens in low and middle income countries. Twenty six studies were included. Ten of these were RCTs and 16 were observational studies. The authors found that rates of eclampsia were usually < 5% even when magnesium sulphate was given for eclampsia. Moreover, when dosing varied from standard regimens almost all reduced the dose or duration of treatment because of concerns about maternal safety, cost or resource availability. Authors concluded that further studies to identify the minimum effective dosage of magnesium sulphate for the management of pre-eclampsia and eclampsia are required, as are studies investigating whether magnesium sulphate loading can be safely given in the community.

A number of RCTs were identified which investigated magnesium sulphate. One RCT[62] randomised 48 women with gestational hypertension or mild pre-eclampsia at 34 weeks gestation or greater to magnesium sulphate or placebo. A significant decrease in fetal umbilical artery and middle cerebral artery pulsatility index were found with magnesium sulphate. Another RCT[90] compared the effect of preoperative magnesium sulphate infusion in women with moderate pre-eclampsia. Fifty women were randomised to magnesium or control. Overall, serum cardiac troponin (cTn) levels were comparable between the magnesium group and control group. An RCT[91] also randomised 60 pre-eclamptic women to two different maintenance doses of magnesium sulphate: 2g/hour or 1g/hour. The authors found that the 2g/hour maintenance dose was more likely to attain the therapeutic level of magnesium compared to the 1g/hour dose. Furthermore, no difference between the two groups was found for maternal and neonatal outcomes.

Another RCT[92] was also identified which investigated low dose magnesium sulphate for the control of eclamptic fits. Thirty-nine women were randomised to low dose magnesium sulphate or a standard regimen. The authors found low dose magnesium sulphate was as effective as the standard regimen.

The last RCT[93] also looked at a shortened postpartum course of magnesium sulphate for eclamptic fits. Ninety eight eclamptic women were randomised to a shortened postpartum course of magnesium sulphate or to the standard regimen. Results showed that the shortened course was as effective as the standard regimen for the management of eclampsia.

Administration of Magnesium Sulphate

In an RCT[94] 300 women with pre-eclampsia and proteinuria >1+ (30 mgdL) were randomised to 24 hours of magnesium sulphate administered by the Springfusor pump or by standard hospital practice. In the pump arm fewer women stopped treatment due to adverse effects, toxicity, oliguria or renal failure. Furthermore, significantly less pain was felt by the women using the pump.

Postpartum curettage

The effect of immediate postpartum curettage of the endometrium for pre-eclampsia and eclampsia was investigated in an RCT[95]. Pre-eclamptic or eclamptic women (n= 420) were

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randomised to immediate postpartum curettage or a control group. At follow-up, significant improvements for mean arterial blood pressure and platelet count were found at 6,12 and 24 hours after delivery in the curettage group. Furthermore, curettage was found to accelerate recovery from pre-eclampsia and eclampsia.

The use of magnesium sulphate for 12 hours and 24 hours in postpartum women with severe pre-eclampsia was investigated in an RCT[96]. Women (n=120) were randomised to magnesium sulphate for either 12 hours or 24 hours. The authors found that 12 hour magnesium sulphate was associated with less drug exposure, significant reductions in indwelling bladder catheters, time to ablation and the time to maternal contact with the newborn. However, clinical outcomes were similar between groups.

Another RCT[97] was identified that also investigated if magnesium sulphate prophylaxis was needed for up to 24 hours postpartum in women with pre-eclampsia. One hundred and fifty women with severe pre-eclampsia were randomised to continue receiving or discontinue magnesium sulphate after 6 hours postpartum. It was found that for women with a low risk of postpartum eclampsia, discontinuation was as effective for seizure prophylaxis as the continuation of magnesium over 24 hours. Furthermore, a significant reduction in doctor and nurse time was found in the discontinuation group.

6-year surveillance summary

Magnesium Sulphate

A systematic review[98] (5 trials, n=8909) found that magnesium sulphate significantly reduced the rate of eclampsia and did not affect blood loss intrapartum and postpartum in women with pre-eclampsia undergoing caesarean delivery. The findings indicated that it may be safe to continue antenatal magnesium sulphate treatment in the intrapartum and postpartum periods.

Magnesium Sulphate

A systematic review[99] (5 non-randomised studies) found that, compared with standard regimens, lower-dose regimens of magnesium sulphate were found to be non-inferior to standard dose regimens in terms of preventing seizures in the treatment of pre-eclampsia and eclampsia. However, the evidence was obtained from low to very low quality studies and further high quality studies were recommended.

A systematic review[100] (28 studies) found that the profiles of Zuspan and Pritchard regimens of magnesium sulphate indicated that the minimum effective serum magnesium concentration for eclampsia prophylaxis is lower than the generally accepted level. Exposure-response studies to identify effective alternative dosing regimens were recommended to target concentrations achievable by these standard regimens.

Corticosteroids for HELLP syndrome

A systematic review[101] (15 studies, n=1462) found that corticosteroid administration to HELLP patients improved platelet count, and the serum levels of lactic dehydrogenase and alanine aminotransferase levels, and reduced hospital/intensive care stay and blood transfusion rate, but was not significantly associated with better maternal mortality and overall morbidity. It should be noted that the meta-analysis inappropriately combined randomised and non-randomised studies, and sample sizes of individual studies were small. Further trials were recommended.

Topic expert feedback

Topic expert feedback indicated that betamethasone is not licensed for women with HELLP.

The 3 dexamethasone injection summary of product characteristics (SPCs) are broader in their indication and could be interpreted as covering this indication. However, the SPCs for dexamethasone and betamethasone highlight that they cross the placenta and abnormalities have been found in animal studies and should only be used in pregnancy if the benefits outweigh the risks to the mother and child.

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Impact statement
Magnesium sulphate

The evidence from previous surveillance reviews was considered unlikely to impact on guideline recommendations.

The new evidence supporting low dose regimens of magnesium sulphate, and lower serum magnesium concentrations, to prevent seizures is based on low quality evidence with unconfirmed sample sizes. Further robust exposure-response studies may be needed to establish effective alternative dosing regimens to be incorporated into the guideline.

The new systematic review evidence supports the use of magnesium sulphate in women with pre-eclampsia undergoing caesarean delivery. This is consistent with NICE guideline CG107, which advises giving intravenous magnesium sulphate to women with severe pre-eclampsia who are in a critical care setting if birth is planned within 24 hours (1.8.1.2).

NICE guideline CG107 advises against using dexamethasone or betamethasone for the treatment of HELLP syndrome (1.8.4.1). The Guideline committee concluded that there is high-quality evidence that corticosteroids used in the management of HELLP syndrome do not improve any clinically important outcomes either antenatally or postnatally. The new systematic review evidence supports the use of corticosteroids for some outcomes but not maternal mortality or morbidity. However, the meta-analysis inappropriately combined randomised and non-randomised studies, and sample sizes of included studies were small. It is therefore unlikely to impact on recommendation 1.8.4.1.

New evidence is unlikely to change guideline recommendations.

Breastfeeding

107-16 **How should women, who were hypertensive in pregnancy, especially for those who wish to breastfeed, be managed in the postnatal period?**

Recommendations derived from this question

1.9.1.1 In women who still need antihypertensive treatment in the postnatal period, avoid diuretic treatment for hypertension if the woman is breastfeeding or expressing milk.

1.9.1.2 Tell women who still need antihypertensive treatment in the postnatal period that the following antihypertensive drugs have no known adverse effects on babies receiving breast milk:

- labetalol†
- nifedipine†
- enalapril†
- captopril†
- atenolol†
- metoprolol†.

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1.9.1.3 Tell women who still need antihypertensive treatment in the postnatal period that there is insufficient evidence on the safety in babies receiving breast milk of the following antihypertensive drugs:

- ARBs
- amlodipine
- ACE inhibitors other than enalapril† and captopril†.

1.9.1.4 Assess the clinical wellbeing of the baby, especially adequacy of feeding, at least daily for the first 2 days after the birth.

Surveillance decision

This review question should be updated.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[102] was identified which looked at the prevention and treatment of postpartum hypertension. Nine trials were included. The authors found that for women with pre-eclampsia, postnatal furosemide decreased the need for postnatal antihypertensive therapy in hospital. However, they suggest that more data is needed before this practice can be recommended. No reliable data was found for the management of women with postpartum hypertension.

The new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
Topic expert feedback highlighted that the NICE guideline recommendations 1.9.1.2 and 1.9.1.4 and the full guideline are slightly discrepant and not precise regarding care of the baby, e.g. monitoring and time of discharge. This is because there was no firm evidence at the time of guideline development but the Guideline Committee considered it sufficiently important to discuss and make general recommendations.

The recommendation from the NICE version of the guideline does not specifically list neonatal hypoglycaemia as an adverse effect when there is maternal antihypertensive treatment in pregnancy or whilst breast feeding. The guidance also states that mothers should be informed that there are no known adverse effects for the breast fed baby of a mother taking antihypertensives.

However, in the full guideline it is noted that the guideline development group discussed the potential adverse neonatal effects of the complications of hypertension in pregnancy and its treatment, and this led to the recommendation that the clinical wellbeing of the baby, especially adequacy of feeding, be assessed at least daily for the first 2 days after birth, and clinical monitoring "would possibly" include blood glucose monitoring.

The topic expert stated that provider Trusts are not clear how to interpret these recommendations, and this may place babies at risk of undetected hypoglycaemia.

The topic expert was not aware of new evidence which would aid further discussion, but considered it necessary that the wording requires review to reduce discrepancy.

Impact statement
No new evidence was identified that would affect recommendations.

However, topic expert feedback indicated that the wording of recommendations 1.9.1.2 and 1.9.1.4 requires review due to discrepancies between the NICE guideline and the full guideline. The wording of these

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recommendations may therefore require review.

New evidence identified that may change current recommendations.

Advice and follow-up care at transfer to community care

107-17 **What advice should be given to women who have had hypertension in pregnancy at discharge from maternity care?**

Recommendations derived from this question

1.10.1 Long-term risk of cardiovascular disease

1.10.1.1 Tell women who have had gestational hypertension or pre-eclampsia, and their primary care clinicians, that these conditions are associated with an increased risk of developing high blood pressure and its complications in later life.

1.10.2 Long-term risk of end-stage kidney disease

1.10.2.1 Tell women with a history of pre-eclampsia who have no proteinuria and no hypertension at the postnatal review (6–8 weeks after the birth) that although the relative risk of end-stage kidney disease is increased the absolute risk is low and no further follow-up is necessary.

1.10.3 Thrombophilia and the risk of pre-eclampsia

1.10.3.1 Do not routinely perform screening for thrombophilia in women who have had pre-eclampsia.

1.10.4 Risk of recurrence of hypertensive disorders of pregnancy

1.10.4.1 Tell women who had gestational hypertension that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 6 (16%) pregnancies to about 1 in 2 (47%) pregnancies
- pre-eclampsia in a future pregnancy ranges from 1 in 50 (2%) to about 1 in 14 (7%) pregnancies.

1.10.4.2 Tell women who had pre-eclampsia that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 8 (13%) pregnancies to about 1 in 2 (53%) pregnancies
- pre-eclampsia in a future pregnancy is up to about 1 in 6 (16%) pregnancies
- pre-eclampsia in a future pregnancy is about 1 in 4 (25%) pregnancies if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.

1.10.5 Inter-pregnancy interval and recurrence of hypertensive disorders of pregnancy

1.10.5.1 Tell women who have had pre-eclampsia that there is no additional risk of recurrence with inter-pregnancy interval up to 10 years.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6 of the full guideline.

1.10.6 Body mass index and recurrence of hypertensive disorders of pregnancy

1.10.6.1 Advise women who have had pre-eclampsia to achieve and keep a BMI within the healthy range before their next pregnancy (18.5–24.9 kg/m2, 'Obesity', NICE clinical guideline 43).

Surveillance decision

This review question should be updated.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
Risk factors
Prior pre-eclampsia as a risk factor

A secondary analysis[103] of data in women with prior pre-eclampsia enrolled in an RCT was identified. Six hundred and six pregnancies were studied to evaluate the frequency and type of pre-term birth in these women. Results showed that women with prior pre-eclampsia were at high risk of pre-term birth and were at high risk for small for gestational age infants.

Cardiovascular risk factors

Biochemical cardiovascular risk factors after hypertensive pregnancy disorders were examined in a meta-analysis[104]. Twenty two studies were included. Results showed that women with previous hypertensive pregnancy disorders had higher glucose, insulin, triglycerides, total cholesterol, HDL-C and LDL-C levels after pregnancy than women with previous normotensive pregnancies.

Another meta-analysis[105] looked at cardiovascular disease risk in women with pre-eclampsia. Case-control and cohort studies were included (n=50). Results showed that women with a history of pre-eclampsia or eclampsia were at significantly increased odds of fatal or diagnosed CVD, cerebrovascular disease and hypertension. However, in women with pre-eclampsia, pre-term delivery was not found to be associated with an increased risk of a future cardiovascular event.

A secondary analysis[106] of the HYPITAT trial was conducted. Cardiovascular risk factors in both the induction of labour ad expectant monitoring groups were examined at 2.5 years postpartum. The prevalence of hypertension and metabolic syndrome, systolic and diastolic blood pressure, BMI waist circumference, glucose, HbA1C, insulin, HOMA score, lipids, HsCRP-levels and micro albumin were found to be comparable between groups.

Arterial stiffness

A meta-analysis[107] investigated the association between arterial stiffness and pre-eclampsia. It included 23 studies. Significant increases in the measurements of arterial stiffness were found in women with pre-eclampsia compared to those with gestational hypertension.

Hypertriglyceridemia

A meta-analysis[108] evaluated the relationship between hypertriglyceridemia and pre-eclampsia. From the 29 case-control and cohort studies included it was found that hypertriglyceridemia was associated with and precedes the onset of pre-eclampsia.

6-year surveillance summary
Risk factors
Polymorphism

A systematic review[109] (11 studies) identified a significant association between II/I polymorphism I allele and increased risk of hypertension under allelic and homozygous genotypic models, suggesting predictive value for these biomarkers. It should be noted that the association was stronger in the Asian population.

A systematic review[110] (45 studies, n=10,236 subjects) found that the ACE gene insertion/deletion polymorphism was associated with the risk of pregnancy-induced hypertension.

Assisted reproduction

A systematic review[111] (39 studies n=146,008 live births) found that multiple pregnancies conceived by assisted reproductive techniques were associated with higher risks of pregnancy-related complications and adverse pregnancy outcomes, including pregnancy-induced hypertension.

Air pollution

A systematic review[112] (10 studies) found an increased risk of all hypertensive disorders in pregnancy to be associated with exposure ambient air pollution during the entire pregnancy (NO2), and during the first trimester (CO and O3).

Magnesium and calcium

A systematic review[113] (16 studies) found that higher total energy and lower magnesium and calcium intake measured during pregnancy were identified as risk factors for hypertensive disorders during pregnancy.

Zinc

A systematic review[114] (17 observational studies) evaluated the association between serum zinc level and preeclampsia. Results indicated that serum zinc level in PE patients is significantly lower than that in healthy pregnancy controls.

A systematic review[115] (13 studies, 11 case-control studies and 2 cross-sectional studies; n=445 pre-eclampsia cases and n=568 healthy controls) indicated that zinc level in pre-eclampsia patients was significantly lower than that of healthy, pregnant women. However, subgroup analysis showed that the association was significant in Asian patients but not in European patients.

Vitamin levels

A systematic review[116] (64 studies) found that vitamins A, C, and E were significantly lower in women for overall preeclampsia, but not for mild or severe pre-eclampsia subtypes. However, the small, low-quality observational studies included in the review limited the strength of the findings.

Antenatal Depression

A systematic review[117] (12 studies, n=8400) found that antenatal depressive symptoms were associated with a moderately increased risk of an operative delivery and preeclampsia.

Periodontal disease

A systematic review[118] (11 studies, n=1118) found that maternal periodontal disease was an independent predictor of pre-eclampsia in pregnant women.

Vitamin levels

HIV positivity

A systematic review[119] (28 studies) found no significant association between HIV positivity and pregnancy-induced hypertension, pre-eclampsia, or eclampsia. However, the high risk of bias within most studies limited the findings and further research was recommended.

Noise exposure

A systematic review[120] (29 studies) found that women exposed to high noise levels (in most of the studies > 80 dB) during pregnancy were at a significantly higher risk for having gestational hypertension amongst other adverse maternal and fetal outcomes.

Iron

A systematic review[121] (26 studies, n=1468) found that a high serum iron level was associated with an increased risk of hypertensive disorders during pregnancy, especially gestational hypertension and preeclampsia.

Organ donors

An observational study[122] (n=85) found that gestational hypertension or pre-eclampsia was more likely to be diagnosed in kidney donors than in matched non-donors with similar indicators of baseline health.

Risk of recurrence

An individual participant data (IPD) metaanalysis[123] (n=99,415 women) found that among women that experienced hypertension in pregnancy, the recurrence rate in a next pregnancy was relatively low, and the course of disease was milder for most women with recurrent disease. For women with gestational hypertension at the index pregnancy, there was a 14.5% recurrence rate of gestational hypertension, a 7.1% recurrence of pre-eclampsia and 0.1% HELLP.

For women with pre-eclampsia at the index pregnancy, there was a 6% recurrence rate of gestational hypertension, a 16% recurrence of pre-eclampsia and 0.2% HELLP.

However, it should be noted that the primary outcome of the meta-analysis was recurrence at the next subsequent pregnancy, as distinct

from any subsequent pregnancy as was used in the NICE guideline CG107.

A systematic review[124] (12 studies) found that women with a history of hypertensive pregnancy disorders had a higher homocysteine level compared with women with a history of uncomplicated pregnancies. This suggested a persistent endothelial alteration after pregnancies complicated by hypertensive disorders. It should be noted that the sample sizes of included studies were not reported in the abstract.

Topic expert feedback
An observational study was cited, relating the risk factor of kidney donor status[122] and is included in the evidence summary. No comments were made relating to this intervention.

Topic expert feedback indicated that the new IPD meta-analysis evidence on risk of recurrence of hypertensive disorders is an important good quality large review of information on recurrence of help to clinicians and women.

Impact statement
The new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

Risk factors

The new evidence suggests that the following are all risk factors for hypertensive disorders during pregnancy:

- multiple pregnancy following assisted reproduction
- air pollution
- dietary energy intake
- vitamin and mineral levels (magnesium, calcium, iron vitamin A,C and E)
- antenatal depression
- periodontal disease
- noise exposure
- kidney donor status.

However, the evidence was largely based on small observational studies, or systematic reviews that did not report the sample sizes or study quality of included studies in the abstract. Consequently, further research may be needed to establish a definite impact on the guideline in terms of adding additional risk factors to recommendation 1.4.1.2.

The evidence from the previous surveillance review for cardiovascular risk factors was considered to be inconclusive, with further research potentially required into the association between previous hypertensive disorders in pregnancy and CVD risk before consideration for the guideline.

Risk of recurrence

The new IPD evidence indicating a relatively low recurrence rate of hypertension in pregnancy in a next pregnancy has a potential impact on recommendations 1.10.4.1 and 1.10.4.2. This potential impact is supported by topic expert feedback.

For women with gestational hypertension at the index pregnancy, (recommendation 1.10.4.1), new evidence indicates a 14.5% recurrence rate of gestational hypertension, a 7.1% recurrence of pre-eclampsia and 0.1% recurrence of HELLP. Recommendation 1.10.4.1 advises telling women with gestational hypertension that recurrence rate of gestational hypertension is 16%-47% and recurrence rate of pre-eclampsia is 2%-7%. There is therefore a potential impact on the guideline to review the recommended recurrence rates for both gestational hypertension (14.5% vs 16%-47%) and pre-eclampsia (7.1% vs 2%-7%).

For women with pre-eclampsia at the index pregnancy, (recommendation 1.10.4.2), there was a 6% recurrence rate of gestational hypertension, a 16% recurrence of pre-eclampsia and 0.2% HELLP. Recommendation 1.10.4.2 advises telling women who had pre-eclampsia that recurrence rate of gestational hypertension is 13%-53% and recurrence rate of pre-eclampsia is 16%. There is therefore a potential impact on the guideline to review the recommended recurrence rate for gestational hypertension (6% vs 13-53%) but not for pre-eclampsia (16% vs 16%).

However, it should be noted that the primary outcome of the IPD meta-analysis was recurrence at the next subsequent pregnancy, as distinct from the outcome of recurrence at any subsequent pregnancy, which was used in the guideline.

The new evidence indicating that women with a history of hypertensive pregnancy disorders may have a higher homocysteine level did not

report the sample sizes of included studies in the abstract and therefore may require further evidence to establish an impact on the guideline.

New evidence identified that may change current recommendations.

Research recommendations

RR – 01 How clinically and cost effective is calcium supplementation (compared with placebo) for the prevention of pre-eclampsia in women at both moderate and high risk of pre-eclampsia?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
Calcium
An updated Cochrane systematic review[125] assessed the effects of calcium supplementation during pregnancy. Fourteen studies met the inclusion criteria. Calcium supplementation was found to significantly reduce pre-eclampsia risk especially in women with low calorie diets. Furthermore, calcium supplementation was found to reduce preterm birth and the occurrence of the composite endpoint of maternal death or serious morbidity. However, the authors suggested that the current evidence is limited since the included studies were small and tended to be at high risk of bias. More large high quality trials are needed.

The effects of calcium supplementation during pregnancy were assessed in a meta-analysis of RCTs[126]. Fifteen RCTs were included. The results indicated that calcium supplementation reduced the risk of pre-eclampsia, severe pre-eclampsia, maternal mortality and severe morbidity and pre-term birth. However, the intervention was found to have no effect on eclampsia incidence or perinatal mortality and was found to non-significantly increase the risk of urolithiasis.

A systematic review[127] also looked at the impact of low dose calcium supplementation on pre-eclampsia risk. Eighteen trials were included. Results showed that pre-eclampsia was reduced with low dose calcium with or without co-supplements.

Two RCTs also investigated calcium. The first[128] evaluated calcium plus low dose aspirin in women at high risk of pre-eclampsia. Pregnant women (n=42) were randomised to calcium plus low dose aspirin or placebo for nine weeks. It was found that the intervention significantly increased total antioxidant capacity and total glutathione but had no effect on serum insulin levels or HOMA-IR score. Furthermore, a significant difference was found in serum high sensitivity C-reactive protein in the intervention group when compared to placebo. The second RCT[129] randomised 49 pregnant women who were at risk of pre-eclampsia to calcium-vitamin D supplements or to a placebo for nine weeks. Results showed that calcium-vitamin D supplementation decreased fasting plasma glucose and triglyceride levels compared to placebo. However, the intervention had no effect on serum total cholesterol, LDL-C or HDL-C.

The new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

6-year surveillance summary
A systematic review[23] (4 studies, n=unreported in abstract) found that calcium supplementation during pregnancy reduced the risk of hypertension. However, there was no reduction in the risk of severe gestational hypertension,

pre-eclampsia, severe pre-eclampsia, preterm birth and low birthweight.

A further systematic review[24] found that calcium supplementation in pregnancy reduced the overall risk of pre-eclampsia in 10 trials (n = 24,787). However, potential publication bias and a lack of large trials limited the impact of the results.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggests that calcium is beneficial for the prevention of pre-eclampsia. CG107 does not currently recommend calcium. This is because the original Guideline Committee felt that most of the evidence was in low-risk women and was from small studies. They also suggested that the benefit of calcium may be greater in women who were deficient in dietary calcium which is not the case in the UK. The new evidence is also from small studies and the evidence provided by the Cochrane review and other systematic reviews is limited due to the inclusion of small, methodologically flawed studies. As such, further well designed large studies may be needed in this area before calcium can be considered for inclusion in the guideline.

New evidence is unlikely to impact on the guideline.

RR – 02 How should significant proteinuria be defined in women with hypertension during pregnancy?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
A systematic review[130] was identified that included 16 studies (n=6749). This showed that proteinuria was a poor predictor of complications in women with pre-eclampsia.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The Evidence update concluded that the evidence was supportive of CG107 which states that quantification of proteinuria in women with pre-eclampsia does not need to be repeated after confirmation of “significant proteinuria”.

No new evidence was identified through the 4 or 6-year surveillance that would change this conclusion.

The ongoing DAPPA trial compares methods of quantifying proteinuria in diagnosing pre-eclampsia. This trial is due to complete and publish in 2017 and will be monitored by the NICE Surveillance team.

New evidence is unlikely to impact on the guideline.

RR – 03 What is the role of assessing haematological or biochemical parameters at diagnosis of gestational hypertension and during surveillance of gestational hypertension?

No new information was identified at any surveillance review.

This research recommendation will be considered again at the next surveillance point.

RR – 04 When should women who have pre-eclampsia with mild or moderate hypertension give birth?

No new information was identified at any surveillance review.

The ongoing PHOENIX trial is relevant to this research recommendation and will be monitored by the NICE Surveillance team. The trial is addressing the uncertainty regarding the timing of delivery for pre-eclampsia between 34 to 37 weeks.

This research recommendation will be considered again at the next surveillance point.

RR – 05 How safe are commonly used antihypertensive agents when used by women who are breastfeeding?

No new information was identified at any surveillance review.

This research recommendation will be considered again at the next surveillance point.

RR – 06 What is the clinical and cost effectiveness of aspirin prophylaxis for the prevention of pre-eclampsia in women with at least two moderate risk factors?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
Antiplatelet agents
A meta-analysis[131] examined low dose aspirin started early in pregnancy on the incidence of pre-eclampsia. Twenty seven RCTs recruiting women at risk of pre-eclampsia were included (n=11348). Results showed that starting low dose aspirin at 16 weeks or earlier significantly reduced pre-eclampsia incidence when compared to placebo or no treatment. Early low dose aspirin also led to a reduced risk of severe pre-eclampsia, gestational hypertension, and pre-term birth. No statistically significant difference in risk of pre-eclampsia was found between low dose aspirin started after 16 weeks and placebo or no treatment. Furthermore, a significant effect was found between treatment given on or before 16 weeks and intrauterine growth restriction. This effect was not found when aspirin was given after 16 weeks.

A systematic review[132] was also identified. This included 69 systematic reviews, RCTs and observational studies. High quality evidence from a systematic review using aggregate data (59 RCTs of 37,560 women) and a systematic review using individual patient data (31 RCTs, 32,217 women) showed that antiplatelet drugs (primarily low dose aspirin) reduced the risk of pre-eclampsia, death of the baby and premature birth without increasing the risk of bleeding in women at high risk of pre-eclampsia. There was no difference in the impact of aspirin prophylaxis before and after 20 weeks gestation.

4-year surveillance summary
Aspirin alone
The benefits and harms of low dose aspirin for preventing morbidity and mortality from pre-eclampsia in high risk women was investigated in a systematic review[133]. Twenty one RCTs and two observational studies were included. Results showed that low dose aspirin reduced

the risk of pre-eclampsia by 2%-5%, reduced the risk of intrauterine growth restriction by 1%-5% and reduced preterm birth risk by 2%-4%.

An individual patient meta-analysis[134] also investigated low dose aspirin. Data on 268 IVF pregnancies treated with preconceptionally started low dose aspirin or placebo were analysed. No significant difference in hypertensive pregnancy complications and preterm delivery between the intervention and control groups for both twin and single pregnancies was found.

An RCT[135] randomised 152 women at high risk of pre-eclampsia to either aspirin or placebo at 12 to 14 weeks of gestation. It was found that low dose aspirin did not reduce the rate of pre-eclampsia, gestational hypertension, early on-set pre-eclampsia or severe pre-eclampsia. Another RCT[136] also investigated low dose aspirin for the prevention of complications in pregnancy. High risk women (n=350) were randomised to placebo or low dose aspirin upon awakening, 8 hours after waking or at bedtime. Results showed that low dose aspirin ingested at bedtime or after 8 hours of waking significantly reduced blood pressure. Pre-eclampsia, pre-term birth, intrauterine growth retardation and gestational hypertension were also significantly reduced with the intervention. In addition, there was no increased risk of haemorrhage either before or after delivery with the intervention relative to the placebo.

A secondary analysis[137] also explored whether low dose aspirin was more efficacious in preventing pre-eclampsia in non-obese women or when initiated before 16 weeks gestation. From the analysis of 2503 women, low dose aspirin was not more effective when initiated < 16 weeks compared to >/= 16 weeks and was not more efficacious in non-obese women compared to obese women.

Aspirin plus calcium for preventing pre-eclampsia
A pilot RCT[138] was identified which investigated aspirin plus calcium for the prevention of pre-eclampsia in pregnant women with chronic hypertension and with abnormal uterine artery Doppler at 20-27 weeks gestation. Forty-nine women were randomised to placebo or aspirin plus calcium daily until delivery. Combined supplementation led to a nonsignificant decrease in fetal growth restriction and superimposed pre-eclampsia incidence. No difference was seen between groups for rate of preterm birth.

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

No new evidence was identified at the 6-year surveillance review that would affect recommendations.

New evidence is unlikely to impact on the guideline.

RR – 07 Which antihypertensive agent is best for use in women with chronic hypertension during pregnancy?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
See 107-03

4-year surveillance summary
See 107-03

6-year surveillance summary (2016)
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Overall, the new evidence identified at the 4-year surveillance review on antihypertensive

agents was considered unlikely to impact on guideline recommendations.

No new evidence was identified at the 6 year surveillance review that would affect recommendations.

New evidence is unlikely to impact on the guideline.

RR – 08 Is uterine artery Doppler velocimetry of value in the clinical management of women at high risk of pre-eclampsia?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
No relevant evidence was identified.

4-year surveillance summary
Uterine artery Doppler Ultrasound
An individual patient meta-analysis[139] was identified which investigated the value of adding second trimester uterine artery Doppler ultrasound to patient characteristics to identify women at risk of pre-eclampsia. Data from 6708 women were analysed. The findings indicated that the addition of Doppler characteristics of pulsatility index or resistance index and bilateral notching to patient characteristics of blood pressure and BMI improved the identification of women at risk of pre-eclampsia.

A systematic review[140] examined the accuracy with which the uterine artery Doppler in the first trimester predicts pre-eclampsia and fetal growth restriction. Eighteen studies (n=55974) were included. The sensitivity and specificity in the prediction of early onset pre-eclampsia were 47.8% and 92.1% and for early onset fetal growth restriction were 39.2% and 93.1%. For predicting any pre-eclampsia and fetal growth restriction the sensitivities were 26.4% and 15.4% whilst specificities were 93.4% and 93.3%.

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Overall, the new evidence identified at the 4-year surveillance review was considered unlikely to impact on guideline recommendations.

No new evidence was identified at the 6-year surveillance review that would affect recommendations.

New evidence is unlikely to impact on the guideline.

RR – 09 What is the most clinically effective antihypertensive agent for severe pre-eclampsia in a critical care setting?

No new information was identified at any surveillance review.

This research recommendation will be considered again at the next surveillance point.

RR – 10 Does the use of dexamethasone in HELLP syndrome have clinical utility?

New evidence was found but is unlikely to impact on guideline recommendations.

This research recommendation will be considered again at the next surveillance point.

2-year Evidence Update summary
See 107-15

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
See 107-15

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
See 107-15

New evidence is unlikely to impact on the guideline.

RR – 11 What is the long-term outcome of women with gestational hypertension?

No new information was identified at any surveillance review.

This research recommendation will be considered again at the next surveillance point.

References

1. 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 & Neonatal Medicine 23:1456-1460.

2. Vadillo-Ortega 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. BMJ (Clinical research ed.) 342:d2901.

3. Dodd JM, McLeod A, Windrim RC et al. (2013) Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. [Update of Cochrane Database Syst Rev. 2010;(6):CD006780; PMID: 20556769]. Cochrane Database of Systematic Reviews 7:CD006780.

4. Basaran A, Basaran M, and Topatan B. (2010) Combined vitamin C and E supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. Obstetrical & Gynecological Survey 65:653-667.

5. Sep S, Smits L, Prins M et al. (2010) Prediction tests for recurrent hypertensive disease in pregnancy, a systematic review. Hypertension in Pregnancy 29:206-230.

6. Schleussner E, Lehmann T, Kahler C et al. (2014) Impact of the nitric oxide-donor pentaerythrityl-tetranitrate on perinatal outcome in risk pregnancies: a prospective, randomized, double-blinded trial. Journal of Perinatal Medicine 42:507-514.

7. Zhu Q, Yue X, Tian QY et al. (2013) Effect of L-arginine supplementation on blood pressure in pregnant women: a meta-analysis of placebo-controlled trials. Hypertension in Pregnancy 32:32-41.

8. Dorniak-Wall T, Grivell RM, Dekker GA et al. (2014) The role of L-arginine in the prevention and treatment of pre-eclampsia: a systematic review of randomised trials. Journal of Human Hypertension 28:230-235.

9. de Vries JI, van Pampus MG, Hague WM et al. (2012) Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. Journal of Thrombosis & Haemostasis 10:64-72.

10. Allen R, Rogozinska E, Sivarajasingam P et al. (19-8-2014) Effect of diet and life style based metabolic risk modifying interventions on preeclampsia: A meta-analysis. Acta Obstetricia et Gynecologica Scandinavica .

11. Aune D, Saugstad OD, Henriksen T et al. (2014) Physical activity and the risk of preeclampsia: a systematic review and meta-analysis. Epidemiology 25:331-343.

12. Kasawara KT, do Nascimento SL, Costa ML et al. (2012) Exercise and physical activity in the prevention of pre-eclampsia: systematic review. Acta Obstetricia et Gynecologica Scandinavica 91:1147-1157.

13. Zhou SJ, Yelland L, McPhee AJ et al. (2012) Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia. American Journal of Clinical Nutrition 95:1378-1384.

14. Hypponen E.Cavadino. (2014) Vitamin D and Pre-Eclampsia: Original data, systematic review and meta-analysis. Annals of Nutrition and Metabolism 63:331-340.

15. Tabesh M, Salehi-Abargouei A, Tabesh M et al. (2013) Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism 98:3165-3173.

16. Mahdy ZA, Siraj HH, Khaza'ai H et al. (2013) Does palm oil vitamin E reduce the risk of pregnancy induced hypertension? Acta Medica (Hradec Kralove) 56:104-109.

17. Kiondo P, Wamuyu-Maina G, Wandabwa J et al. (21-8-2014) The effects of vitamin C supplementation on pre-eclampsia in Mulago Hospital, Kampala, Uganda: a randomized placebo controlled clinical trial. BMC Pregnancy & Childbirth 14:283.

18. Bullarbo M, Odman N, Nestler A et al. (2013) Magnesium supplementation to prevent high blood pressure in pregnancy: a randomised placebo control trial. Archives of Gynecology & Obstetrics 288:1269-1274.

19. Parrish MR, Martin JN, Jr., Lamarca BB et al. (2013) Randomized, placebo controlled, double blind trial evaluating early pregnancy phytonutrient supplementation in the prevention of preeclampsia. Journal of Perinatology 33:593-599.

20. Salles AM, Galvao TF, Silva MT et al. (2012) Antioxidants for preventing preeclampsia: a systematic review. Thescientificworldjournal 2012:243476.

21. Areia AL, Fonseca E, Areia M et al. (2016) Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. Archives of Gynecology and Obstetrics.293 (1) (pp 81-86), 2016.Date of Publication: 01 Jan 2016. 81-86.

22. Muktabhant B, Lawrie TA, Lumbiganon P et al. (2015) Diet or exercise, or both, for preventing excessive weight gain in pregnancy. [Review][Update of Cochrane Database Syst Rev. 2012;4:CD007145; PMID: 22513947]. Cochrane Database of Systematic Reviews 6:CD007145.

23. An LB, Li WT, Xie TN et al. (2015) Calcium supplementation reducing the risk of hypertensive disorders of pregnancy and related problems: A meta-analysis of multicentre randomized controlled trials. International Journal of Nursing Practice 21:Suppl-31.

24. Tang R, Tang IC, Henry A et al. (2015) Limited evidence for calcium supplementation in preeclampsia prevention: a meta-analysis and systematic review. Hypertension in Pregnancy 34:181-203.

25. Arain N, Mirza WA, and Aslam M. (2015) Vitamin D and the prevention of preeclampsia: A systematic review. Pakistan Journal of Pharmaceutical Sciences.28 (3) (pp 1015-1021), 2015.Date of Publication: 01 May 2015. 1015-1021.

26. De-Regil LM, Palacios C, Lombardo LK et al. (2016) Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews .

27. Perez-Lopez FR, Pasupuleti V, Mezones-Holguin E et al. (2015) Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. [Review]. Fertility & Sterility 103:1278-1288.

28. Salam RA, Zuberi NF, and Bhutta ZA. (2015) Pyridoxine (vitamin B6) supplementation during pregnancy or labour for maternal and neonatal outcomes. [Review][Update of Cochrane Database Syst Rev. 2006;(2):CD000179; PMID: 16625530]. Cochrane Database of Systematic Reviews 6:CD000179.

29. Rumbold A, Ota E, Nagata C et al. (2015) Vitamin C supplementation in pregnancy. Cochrane Database of Systematic Reviews .

30. Rumbold A, Ota E, Hori H et al. (2015) Vitamin E supplementation in pregnancy. [Review][Update of Cochrane Database Syst Rev. 2005;(2):CD004069; PMID: 15846695]. Cochrane Database of Systematic Reviews 9:CD004069.

31. Shim SM, Yun YU, and Kim YS. (2016) Folic acid alone or multivitamin containing folic acid intake during pregnancy and the risk of gestational hypertension and preeclampsia through meta-analyses. Obstetrics & Gynecology Science 59:110-115.

32. Chen B, Ji X, Zhang L et al. (2015) Fish Oil Supplementation does not Reduce Risks of Gestational Diabetes Mellitus, Pregnancy-Induced Hypertension, or Pre-Eclampsia: A Meta-Analysis of Randomized Controlled Trials. Medical Science Monitor 21:2322-2330.

33. Dowswell T, Carroli G, Duley L et al. (2015) Alternative versus standard packages of antenatal care for low-risk pregnancy. [Review][Update of Cochrane Database Syst Rev. 2010;(10):CD000934; PMID: 20927721]. Cochrane Database of Systematic Reviews 7:CD000934.

34. Yi XY, Li QF, Zhang J et al. (2015) A meta-analysis of maternal and fetal outcomes of pregnancy after bariatric surgery. [Review]. International Journal of Gynaecology & Obstetrics 130:3-9.

35. Opray N, Grivell RM, Deussen AR et al. (2015) Directed preconception health programs and interventions for improving pregnancy outcomes for women who are overweight or obese. Cochrane Database of Systematic Reviews .

36. Syngelaki A, Nicolaides KH FAU - Balani J, Balani JF et al. (2016) Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. N Engl J Med 374:13-22.

37. Bramham K, Parnell B, Nelson-Piercy C et al. (2014) Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 348:g2301.

38. You WB, Wolf MS, Bailey SC et al. (2012) Improving patient understanding of preeclampsia: a randomized controlled trial. American Journal of Obstetrics & Gynecology 206:431-435.

39. Nij Bijvank SW and Duvekot JJ. (2010) Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature. Obstetrical & Gynecological Survey 65:341-347.

40. Brown MA, Roberts LM, Mackenzie C et al. (2012) A prospective randomized study of automated versus mercury blood pressure recordings in hypertensive pregnancy (PRAM Study). Hypertension in Pregnancy 31:107-119.

41. Vigil-De GP, Dominguez L, and Solis A. (2014) Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial. Journal of Maternal-Fetal & Neonatal Medicine 27:1291-1294.

42. Abalos E, Duley L, and Steyn DW. (2014) Antihypertensive drug therapy for mild to moderate hypertension during pregnancy.[Update of Cochrane Database Syst Rev. 2007;(1):CD002252; PMID: 17253478]. Cochrane Database of Systematic Reviews 2:CD002252.

43. Duley L, Meher S, and Jones L. (2013) Drugs for treatment of very high blood pressure during pregnancy. [Update of Cochrane Database Syst Rev. 2006;(3):CD001449; PMID: 16855969]. Cochrane Database of Systematic Reviews 7:CD001449.

44. Rezaei Z, Sharbaf FR, Pourmojieb M et al. (2011) Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. Acta Medica Iranica 49:701-706.

45. Firoz T, Magee L, MacDonell K et al. (2014) Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology 121:1210-1220.

46. Kasawara KTB. (2013) Maternal and perinatal outcomes of exercise in pregnant women with chronic hypertension and/or previous preeclampsia: A randomized controlled trial. ISRN Obstetrics and Gynecology 2013 , 2013. Article Number: 857047$ of Publication: 2013..

47. Hamed HO, Alsheeha MA, Abu-Elhasan AM et al. (3-6-2014) Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery. International Journal of Gynaecology & Obstetrics .

48. Stout MJ, Conner SN, Colditz GA et al. (2015) The Utility of 12-Hour Urine Collection for the Diagnosis of Preeclampsia: A Systematic Review and Meta-analysis. [Review]. Obstetrics & Gynecology 126:731-736.

49. Giguere Y, Charland M, Bujold E et al. (2010) Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review. Clinical Chemistry 56:361-375.

50. Zhao L, Bracken MB, Dewan AT et al. (2013) Association between the SERPINE1 (PAI-1) 4G/5G insertion/deletion promoter polymorphism (rs1799889) and pre-eclampsia: a systematic review and meta-analysis. Molecular Human Reproduction 19:136-143.

51. Yang Y, Su X, Xu W et al. (25-7-2014) Interleukin-18 and Interferon Gamma Levels in Preeclampsia: A Systematic Review and Meta-analysis. American Journal of Reproductive Immunology .

52. Shen Y-TY. (2013) Association between 14 bp insertion/deletion polymorphism of HLA-G gene and preeclampsia: A meta-analysis. Chinese Journal of Evidence-Based Medicine 13:955-962.

53. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C et al. (2012) Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology 119:778-787.

54. Metz TD, Allshouse AA, Euser AG et al. (23-4-2014) Preeclampsia in high risk women is characterized by risk group-specific abnormalities in serum biomarkers. American Journal of Obstetrics & Gynecology .

55. Hui D, Okun N, Murphy K et al. (2012) Combinations of maternal serum markers to predict preeclampsia, small for gestational age, and stillbirth: a systematic review. Journal of Obstetrics & Gynaecology Canada: JOGC 34:142-153.

56. Allen RE, Rogozinska E, Cleverly K et al. (2014) Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis. [Review]. European Journal of Obstetrics, Gynecology, & Reproductive Biology 182:194-201.

57. Pergialiotis V, Prodromidou A, Pappa E et al. (2016) An evaluation of calprotectin as serum marker of preeclampsia: a systematic review of observational studies. Inflammation Research 65:95-102.

58. Zhu X-L, Wang J, Jiang R-Z et al. (2015) Pulsatility index in combination with biomarkers or mean arterial pressure for the prediction of pre-eclampsia: Systematic literature review and meta-analysis. Annals of Medicine.47 (5) (pp 414-422), 2015.Date of Publication: 04 Jul 2015. 414-422.

59. Wu P, Van Den Berg C, Alfirevic Z et al. (2015) Early pregnancy biomarkers in pre-eclampsia: A systematic review and meta-analysis. International Journal of Molecular Sciences.16 (9) (pp 23035-23056), 2015.Date of Publication: 23 Sep 2015. 23035-23056.

60. Wu X, Yang K, Tang X et al. (2015) Folate metabolism gene polymorphisms MTHFR C677T and A1298C and risk for preeclampsia: a meta-analysis. Journal of Assisted Reproduction & Genetics 32:797-805.

61. Zeisler H, Llurba E FAU - Chantraine F, Chantraine FF et al. (2016) Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med 374:13-22.

62. Dasgupta S, Ghosh D, Seal SL et al. (2012) Randomized controlled study comparing effect of magnesium sulfate with placebo on fetal umbilical artery and middle cerebral artery blood flow in mild preeclampsia at > 34 weeks gestational age. Journal of Obstetrics & Gynaecology Research 38:763-771.

63. Aparna J. (2013) A randomized, double-blind, comparative trial of nifedipine and methyldopa in moderate pregnancy induced hypertension. Der Pharmacia Lettre 5:274-277.

64. Shekhar S, Sharma C, Thakur S et al. (2013) Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstetrics & Gynecology 122:1057-1063.

65. Raheem IA, Saaid R, Omar SZ et al. (2012) Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG: An International Journal of Obstetrics & Gynaecology 119:78-85.

66. Molvi SN, Mir S, Rana VS et al. (2012) Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Archives of Gynecology & Obstetrics 285:1553-1562.

67. Gui S, Jia J, Niu X et al. (2014) Arginine supplementation for improving maternal and neonatal outcomes in hypertensive disorder of pregnancy: a systematic review. Journal of the Renin-Angiotensin-Aldosterone System 15:88-96.

68. Reid J, Taylor-Gjevre R, Gjevre J et al. (15-4-2013) Can gestational hypertension be modified by treating nocturnal airflow limitation? Journal of Clinical Sleep Medicine 9:311-317.

69. Shekhar S, Gupta N, Kirubakaran R et al. (2016) Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. [Review]. BJOG: An International Journal of Obstetrics & Gynaecology 123:40-47.

70. Gresham E, Bisquera A, Byles JE et al. (2016) Effects of dietary interventions on pregnancy outcomes: a systematic review and meta-analysis. Maternal and Child Nutrition.12 (1) (pp 5-23), 2016.Date of Publication: 01 Jan 2016. 5-23.

71. Vijgen SM, 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 trial). BJOG: An International Journal of Obstetrics & Gynaecology 117:1577-1585.

72. Koopmans CM, Bijlenga D, Groen H et al. (2009) Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 374:979-988.

73. Magee L, von DP, Rey E et al. (2014) 5.6 The Control of Hypertension In Pregnancy Study (CHIPS) randomised controlled trial. Archives of Disease in Childhood Fetal & Neonatal Edition 99:A5-A6.

74. Tajik P, van der Tuuk K, Koopmans CM et al. (2012) Should cervical favourability play a role in the decision for labour induction in gestational hypertension or mild pre-eclampsia at term? An exploratory analysis of the HYPITAT trial. BJOG: An International Journal of Obstetrics & Gynaecology 119:1123-1130.

75. Hofmeyr GJ. (2012) Abdominal decompression for suspected fetal compromise/pre-eclampsia. [Update of Cochrane Database Syst Rev. 2000;(2):CD000004; PMID: 10796079]. Cochrane Database of Systematic Reviews 6:CD000004.

76. Magee LA, Yong PJ, Espinosa V et al. (2009) Expectant management of severe preeclampsia remote from term: a structured systematic review. Hypertension in Pregnancy 28:312-347.

77. Seal SL, Ghosh D, Kamilya G et al. (2012) Does route of delivery affect maternal and perinatal outcome in women with eclampsia? A randomized controlled pilot study. American Journal of Obstetrics & Gynecology 206:484-487.

78. El-Kerdawy H and Farouk A. (2010) Labor analgesia in preeclampsia: remifentanil patient controlled intravenous analgesia versus epidural analgesia. Middle East Journal of Anesthesiology 20:539-545.

79. Schnabel A, Hahn N, and Borscheit J et al. (2012) Remifentanil for labour analgesia: a meta-analysis of randomised controlled trials. European Journal of Anaesthesiology .

80. Yoo KY, Kang DH, Jeong H et al. (2013) A dose-response study of remifentanil for attenuation of the hypertensive response to laryngoscopy and tracheal intubation in severely preeclamptic women undergoing caesarean delivery under general anaesthesia. International Journal of Obstetric Anesthesia 22:10-18.

81. Pournajafian A, Rokhtabnak F, Kholdbarin A et al. (2012) Comparison of remifentanil and fentanyl regarding hemodynamic changes due to endotracheal intubation in preeclamptic parturient candidate for cesarean delivery. Anesthesiology & Pain Medicine 2:90-93.

82. 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 CD008148.

83. Vigil-De GP, Reyes TO, Calle MA et al. (2013) Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. American Journal of Obstetrics & Gynecology 209:425-428.

84. Reyes OA and Gonzalez GM. (2011) Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double-blind randomized controlled trial. Journal of Obstetrics & Gynaecology Canada: JOGC 33:1099-1104.

85. Gris JC, Chauleur C, Molinari N et al. (2011) Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. Thrombosis & Haemostasis 106:1053-1061.

86. Lam GK, Hopoate-Sitake M, Adair CD et al. (2013) Digoxin antibody fragment, antigen binding (Fab), treatment of preeclampsia in women with endogenous digitalis-like factor: a secondary analysis of the DEEP Trial. American Journal of Obstetrics & Gynecology 209:119-6.

87. Tavasoli FS. (2012) Comparison of effects of labetalol and hydralazine in treatment of hypertension in patients with severe preeclampsia. Iranian Journal of Obstetrics, Gynecology and Infertility 15:1-7.

88. Churchill D, Duley L, Thornton JG et al. (2013) Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. [Update of Cochrane Database Syst Rev. 2002;(3):CD003106; PMID: 12137674]. Cochrane Database of Systematic Reviews 7:CD003106.

89. Gordon R, Magee LA, Payne B et al. (2014) Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens. Journal of Obstetrics & Gynaecology Canada: JOGC 36:154-163.

90. Elzayyat NSY. (2014) Effect of preoperative Mg sulfate infusion on serum cardiac troponin (cTn) in moderate preeclamptic undergoing elective cesarean section under spinal anesthesia. Egyptian Journal of Anaesthesia 30:299-303.

91. Charoenvidhya D and Manotaya S. (2013) Magnesium sulfate maintenance infusion in women with preeclampsia: a randomized comparison between 2 gram per hour and 1 gram per hour. Journal of the Medical Association of Thailand 96:395-398.

92. Abdul MA, Nasir UI, Khan N et al. (2013) Low-dose magnesium sulphate in the control of eclamptic fits: a randomized controlled trial. Archives of Gynecology & Obstetrics 287:43-46.

93. Chama CM, Geidam AD, Bako B et al. (2013) A shortened versus standard matched postpartum magnesium sulphate regimen in the treatment of eclampsia: a randomised controlled trial. African Journal of Reproductive Health 17:131-136.

94. Mundle S.Regi. (2012) Treatment approaches for preeclampsia in low-resource settings: A randomized trial of the Springfusor pump for delivery of magnesium sulfate. Pregnancy Hypertension 2:32-38.

95. Ragab A, Goda H, Raghib M et al. (2013) Does immediate postpartum curettage of the endometrium accelerate recovery from preeclampsia-eclampsia? A randomized controlled trial. Archives of Gynecology & Obstetrics 288:1035-1038.

96. Maia SBK. (2014) Abbreviated (12-hour) versus traditional (24-hour) postpartum magnesium sulfate therapy in severe pre-eclampsia. International Journal of Gynecology and Obstetrics 126:260-264.

97. Darngawn L, Jose R, Regi A et al. (2012) A shortened postpartum magnesium sulfate prophylaxis regime in pre-eclamptic women at low risk of eclampsia. International Journal of Gynaecology & Obstetrics 116:237-239.

98. Graham NM, Gimovsky AC, Roman A et al. (2016) Blood loss at cesarean delivery in women on magnesium sulfate for preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine.29 (11) (pp 1817-1821), 2016.Date of Publication: 02 Jun 2016. 1817-1821.

99. Pratt JJ, Niedle PS, Vogel JP et al. (2016) Alternative regimens of magnesium sulfate for treatment of preeclampsia and eclampsia: a systematic review of non-randomized studies. [Review]. Acta Obstetricia et Gynecologica Scandinavica 95:144-156.

100. Okusanya BO, Oladapo OT, Long Q et al. (2016) Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. BJOG: An International Journal of Obstetrics and Gynaecology.123 (3) (pp 356-366), 2016.Date of Publication: 01 Feb 2016. 356-366.

101. Mao M and Chen C. (2015) Corticosteroid Therapy for Management of Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Syndrome: A Meta-Analysis. Medical Science Monitor 21:3777-3783.

102. Magee L and von DP. (2013) Prevention and treatment of postpartum hypertension. [Update of Cochrane Database Syst Rev. 2005;(1):CD004351; PMID: 15674943]. Cochrane Database of Systematic Reviews 4:CD004351.

103. Connealy BDC. (2014) A history of prior preeclampsia as a risk factor for preterm birth. American Journal of Perinatology 31:483-488.

104. Hermes W, Ket JC, van Pampus MG et al. (2012) Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstetrical & Gynecological Survey 67:793-809.

105. Brown MC, Best KE, Pearce MS et al. (2013) Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. European Journal of Epidemiology 28:1-19.

106. Hermes W, Koopmans CM, van Pampus MG et al. (2013) Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: do women's postpartum cardiovascular risk factors differ between the two strategies? European Journal of Obstetrics, Gynecology, & Reproductive Biology 171:30-34.

107. Hausvater A, Giannone T, Sandoval YH et al. (2012) The association between preeclampsia and arterial stiffness. Journal of Hypertension 30:17-33.

108. Gallos ID, Sivakumar K, Kilby MD et al. (2013) Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology 120:1321-1332.

109. Li Y-X, Zhang Q, Shang X-M et al. (2015) Association of Two Well-defined Polymorphisms in Leptin and Leptin Receptor Genes with Hypertension and Circulating Leptin: A Meta-analysis. Archives of Medical Research.46 (1) (pp 38-46), 2015.Date of Publication: 2015. 38-46.

110. Miao H-W and Gong H. (2015) Correlation of ACE gene deletion/insertion polymorphism and risk of pregnancy-induced hypertension: A meta-analysis based on 10,236 subjects. JRAAS - Journal of the Renin-Angiotensin-Aldosterone System.16 (4) (pp 982-994), 2015.Date of Publication: 01 Dec 2015. 982-994.

111. Qin J, Wang H, Sheng X et al. (2015) Pregnancy-related complications and adverse pregnancy outcomes in multiple pregnancies resulting from assisted reproductive technology: a meta-analysis of cohort studies. Fertility & Sterility 103:1492-1508.

112. Hu H, Ha S, Roth J et al. (2014) Ambient air pollution and hypertensive disorders of pregnancy: A systematic review and meta-analysis. Atmospheric Environment.97 (pp 336-345), 2014.Date of Publication: August 01, 2014. -345.

113. Schoenaker DA, Soedamah-Muthu SS, and Mishra GD. (2014) The association between dietary factors and gestational hypertension and pre-eclampsia: a systematic review and meta-analysis of observational studies. [Review]. BMC Medicine 12:157.

114. Ma Y, Shen X, and Zhang D. (2015) The Relationship between Serum Zinc Level and Preeclampsia: A Meta-Analysis. [Review]. Nutrients 7:7806-7820.

115. Zhu Q, Zhang L, Chen X et al. (2016) Association between zinc level and the risk of preeclampsia: a meta-analysis. Archives of Gynecology & Obstetrics 293:377-382.

116. Cohen JM, Beddaoui M, Kramer MS et al. (2015) Maternal Antioxidant Levels in Pregnancy and Risk of Preeclampsia and Small for Gestational Age Birth: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 10:e0135192.

117. Hu R, Li Y, Zhang Z et al. (2015) Antenatal depressive symptoms and the risk of preeclampsia or operative deliveries: a meta-analysis. PLoS ONE [Electronic Resource] 10:e0119018.

118. Huang X, Wang J, Liu J et al. (2014) Maternal periodontal disease and risk of preeclampsia: a meta-analysis. Journal of Huazhong University of Science and Technology Medical:729-735.

119. Browne JL, Schrier VJ, Grobbee DE et al. (1-9-2015) HIV, Antiretroviral Therapy, and Hypertensive Disorders in Pregnancy: A Systematic Review and Meta-analysis. [Review]. Journal of Acquired Immune Deficiency Syndromes: JAIDS 70:91-98.

120. Dzhambov AM, Dimitrova DD, and Dimitrakova ED. (2014) Noise exposure during pregnancy, birth outcomes and fetal development: meta-analyses using quality effects model. Folia Medica (Plovdiv) 56:204-214.

121. Song Q-Y, Luo W-P, and Zhang C-X. (2015) High serum iron level is associated with an increased risk of hypertensive disorders during pregnancy: A meta-analysis of observational studies. Nutrition Research.35 (12) (pp 1060-1069), 2015.Date of Publication: 01 Dec 2015. 1060-1069.

122. Garg AX, Nevis IF FAU - McArthur E, McArthur E FAU - Sontrop J et al. (2015) Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med 372:124-133.

123. van Oostwaard MF, Langenveld J, Schuit E et al. (2015) Recurrence of hypertensive disorders of pregnancy: An individual patient data metaanalysis. American Journal of Obstetrics and Gynecology.212 (5) (pp 624.e1-624.e17), 2015.Date of Publication: 01 May 2015. 624.

124. Visser S, Hermes W, Ket JC et al. (2014) Systematic review and metaanalysis on nonclassic cardiovascular biomarkers after hypertensive pregnancy disorders. [Review]. American Journal of Obstetrics & Gynecology 211:373-379.

125. Hofmeyr GJ, Lawrie TA, Atallah AN et al. (2014) Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems.[Update of Cochrane Database Syst Rev. 2010;(8):CD001059; PMID: 20687064]. Cochrane Database of Systematic Reviews 6:CD001059.

126. Imdad A and Bhutta ZA. (2012) Effects of calcium supplementation during pregnancy on maternal, fetal and birth outcomes. Paediatric and Perinatal Epidemiology 26 Suppl 1:138-152.

127. Hofmeyr GJB. (2014) Low-dose calcium supplementation for preventing pre-eclampsia: A systematic review and commentary. BJOG: An International Journal of Obstetrics and Gynaecology 121:951-957.

128. Asemi Z, Samimi M, Heidarzadeh Z et al. (15-5-2012) A randomized controlled clinical trial investigating the effect of calcium supplement plus low-dose aspirin on hs-CRP, oxidative stress and insulin resistance in pregnant women at risk for pre-eclampsia. Pakistan Journal of Biological Sciences 15:469-476.

129. Asemi Z, Tabassi Z, Heidarzadeh Z et al. (1-4-2012) Effect of calcium-vitamin D supplementation on metabolic profiles in pregnant women at risk for pre-eclampsia: a randomized placebo-controlled trial. Pakistan Journal of Biological Sciences 15:316-324.

130. 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.

131. Bujold E, Roberge S, Lacasse Y et al. (2010) Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstetrics & Gynecology 116:402-414.

132. Duley L. (2011) Pre-eclampsia, eclampsia, and hypertension. Clinical Evidence 2011, 2011..

133. Henderson JT, Whitlock EP, O'Connor E et al. (20-5-2014) Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Annals of Internal Medicine 160:695-703.

134. Groeneveld E, Lambers MJ, Lambalk CB et al. (2013) Preconceptional low-dose aspirin for the prevention of hypertensive pregnancy complications and preterm delivery after IVF: a meta-analysis with individual patient data. Human Reproduction 28:1480-1488.

135. Villa PM, Kajantie E, Raikkonen K et al. (2013) Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. BJOG: An International Journal of Obstetrics & Gynaecology 120:64-74.

136. Ayala DE, Ucieda R, and Hermida RC. (2013) Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. Chronobiology International 30:260-279.

137. Cantu JA, Jauk VR, Owen J et al. (22-7-2014) Is low-dose aspirin therapy to prevent preeclampsia more efficacious in non-obese women or when initiated early in pregnancy? Journal of Maternal-Fetal & Neonatal Medicine 1-0.

138. Souza EV, Torloni MR, Atallah AN et al. (2014) Aspirin plus calcium supplementation to prevent superimposed preeclampsia: a randomized trial. Brazilian Journal of Medical & Biological Research 47:419-425.

139. Kleinrouweler CE, Bossuyt PM, Thilaganathan B et al. (2013) Value of adding second-trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at increased risk for pre-eclampsia: an individual patient data meta-analysis. Ultrasound in Obstetrics & Gynecology 42:257-267.

140. Velauthar L, Plana MN, Kalidindi M et al. (2014) First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound in Obstetrics & Gynecology 43:500-507.