# 6

# Preventing pre-eclampsia and its complications

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**SYNOPSIS**

*There is a considerable literature devoted to the prevention of pre-eclampsia in order to avoid the associated maternal and perinatal complications. However, pre-eclampsia, at least in its non-severe form, may serve some adaptive function in terms of improved neonatal outcomes in the neonatal intensive care unit[1] or neurodevelopmental outcome[2]. Therefore, we have based our preventative recommendations on the prevention of pre-eclampsia and/or the prevention of its associated complications where literature permits.*

*Preventative interventions may be best started before 16 weeks' gestation when most of the physiologic transformation of uterine spiral arteries occurs, or even before pregnancy. Such early intervention has the greatest potential to decrease the early forms of pre-eclampsia that are associated with incomplete transformation of uterine spiral arteries[3].*

*Pregnant women have been classified as being at 'low' or 'increased' risk of pre-eclampsia most commonly by the presence or absence of one or more of the risk markers (see Chapter 5, Table 5.1). Although the strength of evidence around various interventions to prevent pre-eclampsia varies, there is strong evidence that low-risk women who have low dietary intake of calcium (<600 mg/d) may benefit from calcium supplementation (of at least 1 g/d, orally) to prevent pre-eclampsia. High-risk women are recommended to take calcium supplementation (of at least 1 g/d) if calcium intake is low, and are also recommended to initiate low-dose aspirin (75–100 mg/d) at bedtime before 16 weeks of gestation. Widespread implementation of these interventions is recommended to help prevent pre-eclampsia and its complications.*

## WOMEN AT 'LOW RISK'

Women at 'low risk' of pre-eclampsia are most commonly those from unselected obstetric populations and may be nulliparous or multiparous. (Please see Appendix 6.1 for details of individual randomised controlled trials or systematic reviews of randomised controlled trials that reported on the outcomes of pre-eclampsia, gestational hypertension, maternal morbidity, small-for-gestational-age (SGA) infants, or neonatal morbidity such as neonatal intensive care stay.)

### Abstention from alcohol

There are no trials studying the effect of alcohol abstention on the incidence of hypertensive disorders of pregnancy. Reduced consumption is recommended to reduce blood pressure in non-pregnant individuals[4], but in pregnancy,

abstention is recommended as there is no proven safe level of alcohol intake in pregnancy[5].

### Aspirin (low dose)

There is weak evidence that low-dose aspirin can prevent pre-eclampsia in moderate-risk women (RR 0.86, 95% CI 0.79–0.95; 25 trials, 28,469 women)[6]. However, no trials have evaluated the effect of low-dose aspirin started in the first trimester, something that may be more effective among women at increased risk (see Women at increased risk below).

### Calcium

At a population level, there is an inverse relationship between dietary calcium intake and both blood pressure among non-pregnant individuals and the incidence of pre-eclampsia[7]. Dietary calcium intake may mediate this effect by inhibiting parathyroid activity thereby decreasing intracellular calcium and causing vasodilatation[8].

Although one trial found no decrease in pre-clampsia with 1.5 g/d oral calcium supplementation (RR 0.91, 95% CI 0.69–1.19; 357 women)[9], other reviews found that oral calcium supplementation (of at least 1 g/d) decreased the incidence of pre-eclampsia in low-risk women (8 trials, 15,143 women; RR 0.45, 95% CI 0.41–0.83), gestational hypertension (RR 0.71, 95% CI 0.57–0.89; 8 trials, 15,143 women)[7] and preterm birth (RR 0.76, 95% CI 0.60–0.97; 10 trials, 15,275 women)[10]. Maternal death or serious morbidity (which included severe hypertension) is also reduced (RR 0.80, 95% CI 0.65–0.97; 2 trials, 9732 women) which more than offsets the increase in HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome (RR 2.67, 95% CI 1.05–6.82; 2 trials, 12,901 women) reported in the calcium supplementation arms of the two trials that reported HELLP syndrome[10]; it is possible that the blood pressure lowering effect of calcium supplementation permitted more time for pre-eclampsia to progress to HELLP syndrome.

Oral calcium supplementation of <1 g/d has been trialed in mixed populations of women at low and high risk (e.g. pregnant teenage girls, women with previous pre-eclampsia or women with positive roll over test); see Women at increased risk below.

The benefits of calcium supplementation in women at low risk of pre-eclampsia are most likely restricted to women with low calcium intake; potential harms in this population have not been ruled out and in a supplementation trial of 1.5 g/d in The Gambia, calcium treatment was associated with lower bone mineral content throughout lactation[11]. An alternative to supplementation may be to increase dietary calcium intake, by 3–4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

### Dietary changes

A variety of dietary and lifestyle interventions can reduce the risk of pre-eclampsia (overall RR 0.81, 95% CI 0.69–0.94; 18 trials, 8712 women): by dietary change (RR 0.67, 95% CI 0.53–0.85; 6 trials, 2695 women), not but by essential fatty acid supplementation alone (RR 0.92, 95% CI 0.71–1.18; 6 trials, 4579 women) or by mixed interventions of diet, physical activity and lifestyle (RR 0.93, 95% CI 0.66–1.32; 6 trials, 1438 women)[12].

Dietary salt restriction (with confirmed compliance) does not affect the incidence of gestational hypertension (RR 0.98, 95% CI 0.49–1.94; 2 trials, 242 women) or pre-eclampsia specifically (RR 1.11, 95% CI 0.46–2.66; 2 trials, 603 women[13]). No trials were identified of a heart-healthy diet that was associated with a lower risk of pre-eclampsia in a single case–control study[14]. However, there is a strong belief in many jurisdictions that decreasing dietary salt is a prudent action to take, as illustrated by the following quote:

> "We advise her to eat less salt and not to eat oily food, pickles."
>
> Auxiliary Nurse Midwife/Nurse, Belgaum, India (from CLIP Feasibility Study)

Nutritional education counselling was associated with a reduction in preterm birth (RR 0.46, 95% CI 0.21–0.98; 2 trials, 449 women), and a reduction in low birth weight babies (RR 0.04, 95% CI 0.01–0.14; 1 trial, 300 women)[15]. Specifically within undernourished women, nutritional advice was found to increase birth weight (mean difference 489.76, 95% CI 427.93–551.59; 2 trials, 320 women). Balanced protein/energy supplementation in pregnancy did not affect pre-eclampsia incidence (RR 1.48, 95% CI 0.82–2.66; 2 trials, 463 women), but both stillbirth (RR 0.60, 95% CI 0.39–0.94; 5 trials, 3408 women) and SGA babies (RR 0.79,

95% CI 0.69–0.90; 7 trials, 4408 women) were reduced in incidence[15]. High-protein supplementation may have been associated with harm by increasing the risk of SGA babies (RR 1.58, 95% CI 1.03–2.41; 1 trial, 505 women), although weight at 1 year of age did not differ between the high- and low/no supplementation groups[15]. Isocaloric protein supplementation was found to be unlikely to benefit pregnant women or their infants; it did not affect birth weight (mean difference 108.25 g, 95% CI 220.89–437.40, $I^2 = 84\%$) or weekly gestational weight gain (mean difference 110.45 g/week, 95% CI –82.87–303.76, $I^2 = 85\%$; 2 trials, 184 women)[15]. Theoretical concerns about the effect of starvation ketosis on fetal neurodevelopment have led to recommendations that women should not pursue weight-loss dieting in pregnancy[16].

No trials of probiotics were identified, but the consumption of milk-based probiotics was associated with a lower risk of pre-eclampsia in a Norwegian population-based cohort study of 33,399 primiparous women; the decrease was marked for severe pre-eclampsia (aOR 0.79, 95% CI 0.66–0.96; 32,158 women)[17].

A preventative strategy with considerable potential appeal to women is administration of flavanoids, antioxidants found in citrus fruits, dark chocolates and tea. The idea is based on the inverse relationship between higher chocolate intake and lower blood pressure in pregnancy in a prospective cohort study of 2291 women[18]. Two small trials have found conflicting effects of flavanol-rich chocolate on blood pressure in pregnancy; one trial (90 women) found that blood pressure was lower when high-cocoa-content chocolate was ingested from 11 to 13 weeks' gestation[19], whereas another trial (44 women) found that blood pressure (and endothelial function) were unchanged among normotensive women at baseline[20]. Another trial (160 women) has finished recruiting but the impact of the intervention on endothelial function has not yet been reported[21]. We await adequately powered trials that examine the impact of flavonoids on pre-eclampsia or maternal or perinatal morbidity.

### Folate-containing multivitamins

It is accepted that women should take a folate-containing multivitamin when planning pregnancy and into early pregnancy for primary prevention of neural tube and, possibly, other congenital anomalies[22]. However, periconceptional and ongoing regular use of multivitamins has also been associated with prevention of gestational hypertension (1 trial, 138 women)[23] and pre-eclampsia in women with a body mass index (BMI) $<25\,kg/m^2$ (prospective cohort, 1835 women)[24]. The international Folic Acid Clinical Trial (FACT) is focused on women at increased risk of pre-eclampsia, and is discussed below[25].

### Lifestyle changes

Low- to moderate-intensity regular exercise is beneficial for general health reasons to maintain or improve physical fitness (11 trials, 472 women)[26], and observational studies have associated exercise with a reduced risk of pre-eclampsia in a 'dose-dependent' fashion[27–34]. Overweight women who exercised from early pregnancy had improved exercise capacity (1 trial, 132 women)[35], but we were unable to identify trials of exercise for pre-eclampsia prevention among women at low risk.

Greater workload[31,36] and stress have been associated with pre-eclampsia[37], although the quality of studies is not high[38]. We were unable to identify randomised trials of workload reduction to prevent pre-eclampsia, despite this being a common obstetric intervention.

### Micronutrients other than calcium

Micronutrient deficiencies (other than calcium) are common in pregnancy when one takes a global perspective. Deficiencies of magnesium, zinc and pyridoxine have been associated with an increase in hypertensive disorders of pregnancy and/or their complications[39–41].

Magnesium supplementation (various preparations), primarily in women at low risk, did not affect the incidence of pre-eclampsia (RR 0.87, 95% CI 0.58–1.32; 3 trials, 1042 women), preterm birth <37 weeks' gestational age (RR 0.89, 95% CI 0.69–1.14; 7 trials, 5981 women), low birth weight <2500 g (RR 0.95, 95% CI 0.83–1.09; 5 trials, 5577 women) or SGA infants (RR 0.76, 95% CI 0.54–1.07; 3 trials, 1291 women)[40]. A subsequent trial also found that magnesium supplementation (of 300 mg/d from 25 weeks) prevented an increase in diastolic blood pressure during the last weeks of pregnancy (1 trial, 59 women)[42].

Zinc supplementation (20–90 mg elemental zinc), primarily in women of low income, did not affect the hypertensive disorder of pregnancy incidence, although preterm delivery was decreased (RR 0.86, 95% CI 0.76–0.97; 16 trials, 7637 women)[43].

One trial found that antioxidant/phytonutrient supplementation (from plant foods) in the first trimester did not decrease rates of pre-eclampsia in low-risk women (RR 1.22, CI 0.40–3.77)[44].

### Prostaglandin precursors

Diets rich in marine oils are associated with a reduced risk of pre-eclampsia[45]. These marine oils are rich in prostaglandin precursors and may be beneficial by reducing inflammation and vasoconstriction. A systematic review reported that in mixed populations that included both low- and high-risk women, prostaglandin precursors (which included other oils such as evening primrose oil) did not decrease the risk of pre-eclampsia (RR 0.86, 95% CI 0.59–1.27; 6 trials, 2783 women), but they did decrease birth before 34 weeks (RR 0.69, 95% CI 0.49–0.99; 2 trials, 860 women)[45]. A randomised controlled trial assessing the effect of fish oil supplementation in the second half of pregnancy also found no reduction in pre-eclampsia (RR 0.87, 95% CI 0.60–1.25; 2399 women)[46]. It should be noted that given concerns about contaminants such as mercury, increased dietary intake of fish for the purpose of fish oil consumption is not recommended[47].

### Smoking cessation

While it is true that smoking is associated with a reduced risk of pre-eclampsia in observational studies[48–50], smoking also increases the risk of impaired fetal growth and preterm birth[51–53].

Smoking cessation has been shown to decrease the incidence of low birth weight babies (RR 0.82, 95% CI 0.71–0.94; 14 trials, 8562 women) and preterm birth (RR 0.82, 95% CI 0.70–0.96; 14 women, 7852 women)[54]. Although various smoking cessation approaches have been tried, a randomised controlled trial evaluating the effectiveness and safety of nicotine replacement therapy in pregnancy did not show a difference in either pregnancy outcomes or long-term quit rates in pregnancy[55].

### Thiazide diuretics

Thiazide diuretics did not decrease pre-eclampsia (RR 0.68, 95% CI 0.45–1.03; 4 trials, 1391 women) or adverse outcomes, but they did increase maternal side-effects (vs. placebo) in women at low risk of pre-eclampsia (RR 5.81, 95% CI 1.04–32.46; 2 trials, 1217 women)[56].

### Vitamins C and E

Pre-eclampsia is associated with oxidative stress. However, among women at low risk given vitamins C (1000 mg/d) and E (400 international units/day) therapy from either the first or early second trimester, vitamins C and E did not decrease the incidence of pre-eclampsia (RR 0.85, 95% CI 0.48–1.51; 4 trials, 2441 women). In fact, vitamins C and E increased use of any antihypertensive (RR 1.77, 95% CI 1.22–2.57; 2 trials, 4272 moderate- and high-risk women) and antenatal hospital admission for hypertension (RR 1.54, 95% CI 1.00–2.39; 1 trial, 1877 moderate- and high-risk women)[57].

Subsequent trials have confirmed this lack of benefit. A total of 10,514 nulliparous women at low risk for pre-eclampsia were randomly assigned to daily 1000 mg of vitamin C and 400 IU of vitamin E or matching placebo from 9 to 16 weeks until delivery. Intervention was not associated with prevention of severe hypertension (RR 1.07, 95% CI 0.91–1.25) or pre-eclampsia (RR 1.07, 95% CI 0.93–1.24)[58]. Similarly, no significant effect on gestational hypertension (RR 0.99, 95% CI 0.78–1.26) or pre-eclampsia (RR 1.04, 95% CI 0.75–1.44) was observed among 2647 pregnant women randomised to vitamin C and E or placebo[59]. One randomised controlled trial with 299 women evaluating vitamin E therapy (N = 151) versus placebo (N = 148) from early second trimester until delivery found no statistically significant difference in gestational hypertension, but there was a tendency towards a lower incidence of hypertension in the treatment arm (RR 0.36, 95% CI 0.12–1.09)[60]. Another randomised controlled trial with 932 women evaluated 100 mg vitamin C supplementation alone versus placebo from 12 to 22 weeks of gestation and found no difference in the incidence of pre-eclampsia (RR 0.77, 95% CI 0.37–1.56), severe pre-eclampsia (RR 1.25, 95% CI 0.34–4.56), gestational hypertension (RR 0.67, 95% CI 0.43–1.03),

preterm delivery (RR 0.92, 95% CI 0.63–1.34) or low birth weight (RR 1.07, 95% CI 0.72–1.59)[61].

### Vitamin D

Vitamin D may play a protective role against pre-eclampsia through beneficial effects on immune modulation and vascular function[62–64]. A significant relationship between vitamin D deficiency and increased risk of pre-eclampsia has been shown by systematic reviews and meta-analyses of observational studies[65,66]. This represents an area where further studies are required.

### Other interventions for which no recommendation can be made

Interest in supplementation with iron and/or folate (beyond 10 weeks' gestation) stems from the importance of anaemia in developing countries and further progressive anaemia associated with pregnancy[67]. There is insufficient evidence on the effect on pre-eclampsia of either routine (vs. no routine) iron supplementation (usually 60–100 mg elemental iron/day) (1 trial, 47 women) or routine iron with/without folic acid supplementation (1 trial, 48 women)[68].

Pyridoxine has many roles, including neurological development and function. Although in a systematic review, pyridoxine supplementation did not decrease the risk of pre-eclampsia, the trials were of poor quality with poor reporting of substantive outcomes, making it impossible to draw conclusions (oral pyridoxine RR 1.71, 95% CI 0.85–3.45; 2 trials, 1197 women) (pyridoxine lozenges RR 1.43, 95% CI 0.64–3.22; 1 trial, 944 women)[69].

Garlic may lower blood pressure[70], reduce oxidative stress[71] and inhibit platelet aggregation[72], but a systematic review found no clear effect on pre-eclampsia (RR 0.78, 95% CI 0.31–1.93). As only one trial with 100 women was included, further trials are needed to draw any reliable conclusions about garlic and its effect on pre-eclampsia[73].

We were unable to identify trials administering the following agents for primary prevention of pre-eclampsia: vitamin A, selenium, copper and iodine.

It must be noted that in some regions, there is strong interest in traditional medicines for pre-eclampsia prevention. Evidence is lacking to support or refute these practices.

> "About snails, we use the fluid from a snail to prepare traditional medicine to treat patients with high blood pressure . . . we use the snail's fluid to prepare a traditional medicine for them . . . and they would use a teaspoon to take the medicine . . . those that always have high blood pressure . . . people whose blood pressure is always high . . . people like that . . . within 3 months or so . . . they would be lying on a sick bed . . . they would rolling on the floor in pains . . . and be doing all sorts of things . . . so we treat them so that the high blood pressure wouldn't cause complications for them".
>
> Head Traditional Birth Attendant, Yewa South, Nigeria (from CLIP Feasibility Study)

## WOMEN AT INCREASED RISK

Women identified as being at 'increased risk' of pre-eclampsia have been most commonly those with a personal or family history of a hypertensive disorder of pregnancy, chronic medical disease (including hypertension), and/or an abnormal uterine artery Doppler velocimetry before 24 weeks. However, there was variability between studies in inclusion criteria (including use of the roll-over test reflecting increased sensitivity to angiotensin-II) and other characteristics of the population, including ethnicity, parity, socioeconomic status and access to prenatal care. No study identified used only the roll-over test to enroll women.

A growing literature suggests that combining clinical, biochemical and/or ultrasonographic risk markers may better identify women at increased risk of pre-eclampsia (as as discussed in Chapter 5); however, to date no intervention trial has used such an approach to evaluate a preventative therapy[74–76]. The ASPRE trial is doing so for aspirin (150 mg/d at bedtime), as discussed below[77]. (Please see Appendix 6.2 for details of individual randomised controlled trials or systematic reviews of randomised controlled trials that reported on the outcomes of pre-eclampsia, gestational hypertension, maternal morbidity, SGA infants, or neonatal morbidity such as neonatal intensive care stay.)

### Antihypertensive therapy

Antihypertensive therapy does not prevent pre-eclampsia (RR 0.93, 95% CI 0.80–1.08; 23 trials, 2851 women) or the associated adverse perinatal outcomes, but it decreases by half the

incidence of development of severe hypertension (RR 0.49, 95% CI 0.40–0.60; 2 trials, 2558 women)[78]. Antihypertensive therapy cannot be recommended for pre-eclampsia prevention until it can be demonstrated that the decrease in maternal blood pressure is not outweighed by a negative impact on perinatal outcomes[79,80]. (Antihypertensive therapy for treatment of elevated blood pressure is discussed in Chapter 8)

**Aspirin (low dose)**

In women identified as at increased risk of pre-eclampsia based on clinical characteristics, low-dose aspirin results in a small decrease in pre-eclampsia (RR 0.75, 95% CI 0.66–0.85; 18 trials; 4121 women for this outcome), preterm delivery <37 weeks' gestation (RR 0.89, 95% CI 0.81–0.97; $I^2$ 32%; 10 trials, 3252 women for this outcome), perinatal death (RR 0.69, 95% CI 0.53–0.9; 17 trials, 4443 women for this outcome) (40 trials, 33,098 women overall)[6], and intrauterine growth restriction (RR 0.80, 95% CI 0.65–0.99; $I^2$ 36.9%, 13 trials, 12,504 women for this outcome)[81]. There is low level evidence that low-dose aspirin may help to prevent pre-eclampsia (RR 0.67, 95% CI 0.48–0.94; 5 trials, 898 women) in multiple gestations[82]. The ASPRE trial is doing so for aspirin (150 mg/d at bedtime) started in the first-trimester in women identified as being at increased risk[77].

Aspirin does not increase or decrease miscarriage risk[83]. There is no evidence of short- or long-term adverse effects on the mother or newborn.

Who should receive aspirin, in what dose, and when are unclear. Subgroup analyses in meta-analyses suggest a number of important considerations. First, *aspirin is more effective in decreasing pre-eclampsia among women at high risk* (NNT 19, 95% CI 13–34) compared with those at moderate risk (NNT 119, 95% CI 73–333), though a recent meta-analysis did not show any effect of preconceptionally started aspirin in reducing hypertensive pregnancy complications in IVF women[84]. Second, *aspirin may be more effective at decreasing the following outcomes when it is initiated before 16 weeks' gestation: severe pre-eclampsia*[85], preterm pre-eclampsia, preterm delivery, perinatal death and SGA infants[81,86–90]. Preconception-initiated low-dose aspirin was associated with the outcome of higher live birth rates in women with a single documented loss at less than 20 weeks' gestation during the previous year[91]. However, a recent secondary analysis showed that 60 mg of aspirin daily, initiated before or after 16 weeks' gestation was not effective for the prevention of pre-eclampsia[92]. Therefore, *aspirin may be more effective when used at a higher dose*[6,93]. Approximately one-third of pregnant women are both resistant to the effects of 75–80 mg of aspirin and at increased risk of adverse pregnancy outcomes[94,95]. A retrospective controlled study (270 women) suggested that adjusting aspirin dosage based on platelet function testing may improve the effectiveness of aspirin without a demonstrated increase in adverse neonatal outcomes[96]. Furthermore, two randomised controlled trials found that *taking aspirin at bedtime (instead of the morning) resulted in lower blood pressure and fewer adverse pregnancy outcomes* such as pre-eclampsia, SGA babies and preterm birth[97,98]. Finally, *aspirin may be continued until delivery* as was prescribed in most trials; however, some care providers of women in these trials stopped aspirin prior to delivery and the benefits of continuing aspirin throughout the third trimester have also been questioned[99] (see Chapters 8 and 10).

**Calcium**

Oral calcium supplementation (of at least 1 g/d) in high-risk women (e.g. teenagers or women older than 40 years, women with previous pre-eclampsia, women with increased sensitivity to angiotensin II, women with pre-existing hypertension) was found to decrease the incidence of pre-eclampsia (RR 0.22, 95% CI 0.12–0.42; 5 trials, 587 women), gestational hypertension (RR 0.47, 95% CI 0.22–0.97; 4 trials, 327 women) and preterm delivery (RR 0.45, 95% CI 0.24–0.83; 4 trials, 583 women)[7]. Three of the five relevant trials were conducted in low calcium intake populations. No trial included women with previous pre-eclampsia. There were no documented adverse effects of calcium supplementation, but none of these trials of women at high risk of pre-eclampsia reported the outcome of HELLP syndrome. An alternative to supplementation may be an increase in dietary calcium intake, by 3–4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

Oral calcium supplementation of <1 g/d is also effective in mixed populations of women at low and increased risk of pre-eclampsia, but the effect

within each of these populations is not known. The Calcium and Pre-eclampsia (CAP) Study is an ongoing randomised trial of low-dose calcium supplementation among women at high risk of pre-eclampsia)[100].

**Aspirin (low-dose) combined with calcium**

Two small trials (91 women) have looked at the combined effect of low-dose aspirin and calcium supplementation (one <1 g/d[101] and one more than 1 g/d[102]). The combined therapy from 20 to 27 weeks' gestation was associated with a non-significant decrease in pre-eclampsia (52.5% vs. 73.1%, $p = 0.11$) and IUGR (25.0% vs. 4.8%, $p = 0.07$) that may warrant further study, particularly as both therapies are currently recommended individually[102]. In particular, it is not known what the effect would be of supplementation before 16–20 weeks of gestation, and bioavailability studies are required to determine how much aspirin and calcium are actually being absorbed by study participants[102]. The other trial of aspirin and low-dose calcium found that combined therapy was associated with significant improvement in pro-inflammatory factors of highly sensitive C-reactive protein (hs-CRP), plasma total antioxidant capacity (TAC) and total glutathione (GSH)[101].

**Dietary changes**

We were unable to identify trials of dietary salt restriction on the incidence of pre-eclampsia among women at increased risk. Women with pre-existing hypertension who are already following a dietary approached to stop hypertension (DASH) diet may continue this diet during pregnancy, but there is no evidence to support this practice.

We were unable to identify trials of a heart-healthy diet for pre-eclampsia prevention.

Obesity is both a major public health problem and a risk marker for pre-eclampsia. No effect on gestational hypertension (or pre-eclampsia specifically) has been demonstrated when overweight women have received dietary counselling during pregnancy to curb the rate of weight gain (3 trials, 384 women)[15]. No trials have addressed the impact of pre-pregnancy or early pregnancy weight reduction on pre-eclampsia; there are theoretical concerns about the impact of starvation ketosis on fetal neurodevelopment[16].

Garlic may decrease lipid peroxidation and platelet aggregation. One small trial of 100 women at increased risk of pre-eclampsia based on a positive roll-over test found that garlic supplementation in the third trimester of pregnancy reduced the occurrence of gestational hypertension (18% vs. 36%, $p = 0.04$), but not of pre-eclampsia (14% vs. 18%, $p = 0.80$)[103]. Another small trial (N = 235) found that coenzyme Q10 supplementation from 20 weeks until delivery (compared to placebo) reduces the risk of developing pre-eclampsia (14.4% vs. 25%, $p = 0.035$, RR 0.56, 95% CI 0.33–0.96)[104].

**Folate-containing multivitamin**

Periconceptional and ongoing regular use of multivitamins was associated with higher birth weight centiles in a secondary analysis of the Vitamins in Pre-eclampsia (VIP) (vitamin C and E trial) in the UK[105]. Periconceptional use of a folate-containing multivitamin is recommended for all women of child-bearing age for prevention of neural tube and, possibly, other birth defects. The Canadian FACT trial of folic acid 0–1.1 mg versus 4–5.1 mg (4.0 mg folic acid as the intervention) from 10 to 14 weeks for the prevention of pre-eclampsia has recently completed recruitment and the results are anticipated[106].

**Heparin**

Heparin may improve placentally mediated outcomes through anticoagulant and/or potentially non-anticoagulant actions, such as endothelium-dependent vasodilation[107] and/or reversal of the anti-angiogenic actions of explanted placental villi on cultured endothelial cells[108].

A number of small randomised controlled trials have studied prophylactic doses of heparin (mostly low molecular weight heparin (LMWH)) for women with a history of various placental complications in previous pregnancies. The 2013 Cochrane review (9 trials, 979 women) found that prophylactic doses of heparin (of any type) compared with no treatment, decreased perinatal mortality (2.9% vs. 8.6%; RR 0.40, 95% CI 0.20–0.78), preterm delivery before 34 weeks (8.9% vs. 19.4%; RR 0.46, 95% CI 0.29–0.73), and SGA infants (7.6% vs. 19.0%; RR 0.41, 95% CI 0.27–0.61) in women at high risk of placentally mediated complications[109]. In another review focused on only LMWH (6 trials, 848 women),

LMWH, compared with no treatment, reduced the risk of 'severe' or early-onset pre-eclampsia (1.7% vs. 13.4%; RR 0.16, 95% CI 0.07–0.36), preterm delivery before 37 weeks (32.1% vs. 47.7%; RR 0.77, 95% CI 0.62–0.96), and SGA infants (10.1% vs. 29.4%; RR 0.42, 95% CI 0.29–0.59), without a significant effect on perinatal mortality (pregnancy loss >20 weeks 1.9% vs. 5.3%; RR 0.41, 95% CI 0.17–1.02)[110]. In both analyses, a significant decrease in any pre-eclampsia was seen, but there was more between-trial difference in pre-eclampsia incidence than could be expected by chance alone, as was the case in the LMWH analysis for a composite of placentally mediated pregnancy complications (i.e., pre-eclampsia, placenta abruption, SGA infants, or fetal loss after 12 weeks) (18.7% vs. 42.9%; RR 0.52, 95% CI 0.32–0.86). However, a recent trial with 292 women observed no impact of antepartum prophylactic dose dalteparin (5000 IU once daily up to 20 weeks' gestation and twice daily thereafter until at least 37 weeks' gestation) on a composite outcome of severe or early onset pre-eclampsia, SGA infants, pregnancy loss, or venous thromboembolism in women with thrombophilia at high risk of complications (venous thromboembolism, pregnancy loss, or placentally mediated pregnancy complications) in both an intention-to-treat analysis (17.1%, 95% CI 11.4–24.2% vs. 18.9%, 95% CI 12.8–26.3%; risk difference −1.8%, 95% CI −10.6–7.1%) and an on-treatment analysis (19.6% vs. 17.0%; risk difference +2.6%, 95% CI −6.4–11.6%), but there was an increased risk of minor bleeding associated with LMWH (19.6% vs. 9.2%; risk difference 10.4%, 95% CI 2.3–18.4; $p = 0.01$)[111].

Pending the results of larger trials powered for perinatal mortality or severe maternal morbidity, or individual patient data meta-analysis of greater numbers of smaller trials, LMWH for pre-eclampsia prevention should be used cautiously. The independent role of concomitant treatment with aspirin also remains to be elucidated.

LMWH in prophylactic subcutaneous doses is associated with minimal risks for the mother and, theoretically, none for the fetus as it does not cross the placenta. In a meta-analysis of 64 studies (2777 women), major allergic reactions were uncommon (1.2%) and no woman developed heparin-induced thrombocytopaenia. LMWH in prophylactic doses was associated with very low risks of antenatal bleeding (0.42%), intrapartum bleeding (0.92%) and wound haematoma after either Caesarean or vaginal delivery (0.65%)[112]. In the randomised controlled trial cited above, LMWH was associated with an increase in minor bleeding compared with no treatment[111]. LMWH to prevent recurrent early-onset pre-eclampsia and/or IUGR could be stopped at 34–36 weeks' gestation, so the potential side-effects of LMWH intrapartum and postpartum are not as relevant. However, a recent international audit on maternal and fetal safety of tinzaparin (at therapeutic and prophylactic doses), the adjudication committee considered that serious bleeding events (before, during and after delivery) were *probably related* to tinzaparin therapy in 2.3% of pregnancies, and *possibly related* to tinzaparin in 7.7% (1256 pregnancies in 1109 women)[113]. There was no reported spinal haematoma; 10.4% of the women received tinzaparin within 24 hours of epidural or spinal anaesthesia with a median tinzaparin injection to delivery interval of 12.9 hours (range 0–23.5). Osteoporotic fractures occurred in 0.2% of women, although all had other risk factors for osteoporosis. Neonatal haemorrhage did not occur. Major allergic reactions were uncommon (1.8%). No women developed heparin-induced thrombocytopaenia.

### L-arginine

Supplements containing L-arginine and 'antioxidant vitamins' have been shown to reduce diastolic blood pressure[114] or both systolic and diastolic blood pressure, and the incidence of pre-eclampsia in a population at high risk of the condition (2 trials, 672 women)[115,116]. Another systematic review supported that L-arginine supplements reduced the incidence of pre-eclampsia in high-risk women (RR 0.34, 95% CI 0.21–0.55), as well as risk of preterm birth (RR 0.48, 95% CI 0.28–0.81). The protective effect was greater in women with established hypertensive disease (RR 0.21, 95% CI 0.05–0.98)[117]. Data from several small randomised trials suggests that L-arginine given to women with already diagnosed gestational hypertension (with or without proteinuria) or with IUGR can lead to improvement of maternal blood pressure and uteroplacental circulation[118–123].Optimal dosage needs to be defined and large randomised trials are required.

### Lifestyle changes

There are robust epidemiological data that weight gain between pregnancies (even in non-obese

women) is associated with significantly more pre-eclampsia and other pregnancy complications, such as Caesarean delivery and gestational diabetes[124].

Physical activity is associated with a reduced incidence of pre-eclampsia[125,126]. In women at increased risk of pre-eclampsia, it is not known whether exercise (to improve or maintain fitness) is of greater benefit than risk. No impact of exercise was seen on gestational hypertension or pre-eclampsia (2 trials, 45 women), although the trials were small and the confidence intervals were wide[126,127]. Similar results were seen in another small trial of 79 sedentary women with previous pre-eclampsia, among whom walking exercise vs. stretching exercise during pregnancy did not decrease the incidence of pre-eclampsia[128].

Physically demanding work is associated with a higher risk of gestational hypertension and pre-eclampsia (OR 1.60, 95% CI 1.30–1.96; 4 observational studies, 5837 women)[36]. Although workload reduction is a common obstetric intervention, we were unable to identify randomised studies of workload or stress reduction on the incidence of pre-eclampsia. These are unlikely to be forthcoming given the nature of the interventions.

Increased rest at home (varying from 30 minutes to 6 hours/day) in the third trimester of pregnancy decreased the incidence of pre-eclampsia (RR 0.05, 95% CI 0.00–0.83; 1 trial, 32 women for increased rest alone; RR 0.13, 95% CI 0.03–0.51 for rest plus a nutrient supplement; 1 trial, 74 women)[129]. Other substantive outcomes (such as adverse effects of rest and women's views) were not reported. There is a lack of clarity about the definition of bed rest and uncertainty about whether women comply with activity restriction[130].

### Metformin

One trial (N = 105 women) observed that women with polycystic ovarian syndrome (PCOS) randomised to receive metformin (vs. placebo) from the first-trimester of pregnancy showed significant improvement of the uterine artery Doppler pulsatility index to a similar extent as that observed with low-dose aspirin[131]. This trial did not have the power to observe a significant difference in the rate of pre-eclampsia (5.7% with metformin, 5.7% with aspirin, and 11.4% in the placebo group, $p = 0.58$). However, in a secondary analysis of another trial of 400 obese non-diabetic women (BMI >35 kg/m$^2$) randomised to metformin (1–3 g daily, gradually titrated over 4 weeks) or placebo, metformin was associated with a significant decrease in pre-eclampsia (2.0% vs. 8.2%, $p = 0.005$)[132]. Further studies are warranted.

### Micronutrients other than calcium

Magnesium supplementation (various preparations) administered to a mixed population of women at low and high risk in (7 trials, 2689 women) did not decrease the risk of pre-eclampsia, but decreases were seen in preterm birth (RR 0.73, 95% CI 0.57–0.94), low birth weight (RR 0.67, 95% CI 0.46–0.96) and incidence of SGA infants (RR 0.70, 95% CI 0.53–0.93)[40]. However, no conclusions can be drawn because only one included trial was of high quality.

In one trial (100 women), selenium supplementation in the third trimester was reported to decrease gestational hypertension, but this was not defined[133]. Another small trial (166 women) found no significant decrease in the rate of pre-eclampsia[134].

One study found that daily ingestion of a phytonutrient supplement did not decrease rates of pre-eclampsia in high-risk women[135].

We did not identify trials of zinc, pyridoxine, iron (with/without folic acid), zinc, multivitamins with/without micronutrients, vitamin A, iodine, or copper for pre-eclampsia prevention in women at increased risk.

### Prostaglandin precursors

According to the most recent Cochrane systematic review, prostaglandin precursors did not decrease the risk of pre-eclampsia in mixed populations of women at low and high risk (RR 0.87, 95% CI 0.59–1.28; 5 trials, 1683 women)[45]. Birth before 34 weeks was marginally decreased (RR 0.69, 95% CI 0.49–0.99). However, a recent trial including pregnant women with previous pregnancy complications showed that fish oil supplementation was associated with a more advanced gestational age at delivery in low and middle (but not high) fish consumers[136].

### Vitamins C and E

In five trials (3005 women) of women at increased risk of pre-eclampsia for various reasons,

antioxidants (usually combined therapy with vitamins C 1000 mg/d and E 400 international units/day) did not decrease the risk of pre-eclampsia (RR 0.56, 95% CI 0.29–1.11)[56]. These findings were supported by subsequent trials[137,138]. Vitamins C and E have been associated with adverse outcomes, including increased use of intravenous antihypertensive therapy (RR 1.94, 95% CI 1.07–3.53)[139], low birth weight babies (28% (N = 387) vs. 24% (N = 335), RR 1.15, 95% CI 1.02–1.30; 2395 women)[131], fetal loss or perinatal death (RR 2.20, 95% CI 1.02–4.73; 2536 women), preterm prelabour rupture of membranes (RR 1.97, 95% CI 1.31–2.98; 2363 women)[140].

### Nitric oxide donors

Nitric oxide (NO) donors like pentaerithrityl-tetranitrate (PETN) have protective effects on the endothelium. One trial found no decrease in pre-eclampsia from NO-donor PETN, but a decrease in IUGR and/or perinatal death (adjusted RR 0.41, 95% CI 0.18–0.91) and for IUGR (adjusted RR 0.44, 95% CI 0.20–0.97), and preterm birth before 32 weeks' gestational age (adjusted RR 0.20, 95% CI 0.05–0.80)[141].

### Other

Treatment of periodontal disease is not associated with a reduced risk of pre-eclampsia (4 trials)[142,143]. However, it is possible that the type of treatment (scaling vs. chlorexidine mouthwash) could influence its impact, as it has been seen for prevention of preterm birth[144].

## RESOURCE-CONSTRAINED SETTINGS

Pre-eclampsia is ". . . considerably more prevalent in LMICs [low- and middle-income countries] than in affluent communities"[145]. Furthermore, over 99% of pre-eclampsia and eclampsia-related mortality occurs in LMICs, particularly in sub-Sahara Africa and on the Indian subcontinent[146].

Factors that determine the potential impact of an intervention on prevention of pre-eclampsia include its availability, acceptability and cost-effectiveness, as well as the strength of the infrastructure of a health care system. The latter is where LMICs face the greatest challenge. Their unique challenges to intervention implementation include:

- Low rates of antenatal visits and low levels of education in the population, which could be addressed by community engagement and educational activities[146,147].
- Poverty and weak public infrastructure (such as paved roads and available transportation) which prevent access to health care[148]. Addressing these issues will require engagement of government and policy makers.
- A shortage of trained health care workers[146,149]. Major efforts have been directed towards 'task shifting', training and employing community health care workers to play a fundamental role within the health care system in LMICs. In this way, it is hoped that women with hypertensive disorders of pregnancy will receive timely care. This strategy recognises that the majority of pre-eclampsia related deaths in LMICs occur in the community[146].
- A lack of high quality guidance material such as protocols and guidelines[150], something that this book aims to address for the hypertensive disorders of pregnancy.

What follows here are implications relevant to resource-constrained settings for the given recommendations to help prevent pre-eclampsia.

### Aspirin (low dose)

A decision analytic model comparing aspirin prophylaxis (vs. no prophylaxis) in a theoretical cohort of 100,000 pregnant women concluded that it was a more cost-effective strategy than no prophylaxis. Lower costs ($18,720 vs. $18,804) and marginal difference in quality-adjusted life years (26.7417 vs. 26.7422) favours aspirin prophylaxis – a better choice than no prophylaxis[151].

### Calcium supplementation

The impact of calcium in reducing pre-eclampsia is dependent on the baseline calcium intake of the population and pre-existing risk factors[152,153]. Global trends of dietary calcium intake typically show lower intake in LMICs (ranging from 300 to 600 mg/day) compared with high-income countries (e.g., 969 mg for France)[154]. Although these data suggest that calcium supplementation is particularly important for women in developing countries, suboptimal global implementation of this intervention remains. In a study of women

receiving antenatal care in Brazilian public hospitals, over 90% of women consumed less than 1 g of calcium per day, yet less than 6% of women received a prescription for calcium supplements[155]. Similar results were observed in a teaching public hospital in Argentina[156].

Implementation of the recommended high-dose calcium supplementation (1 g calcium/day or more) in settings of low-dietary calcium is problematic to policy-makers and programme managers in LMICs for a number of reasons[157]. Lack of infrastructure challenges the procurement of the preparation, transportation of the heavy tablets, storage, quality control and compliance assurance[158]. The cost implications of the recommended calcium supplementation dose may be a financial barrier; for example, chewable calcium carbonate tablets cost US $3–6/pregnancy[159]. A cost–benefit ratio must be considered by ministries of health in decisions to scale up this intervention[149]. Also, there are potential risks of calcium supplementation, particularly in excess, associated with supplementation in pregnancy, such as HELLP syndrome[7] and rebound postnatal bone demineralisation following supplementation in pregnancy[160].

Potential solutions to the problems discussed include a recently developed micronutrient powder designed to optimise absorption of all its contents (calcium, iron and folic acid)[161] and low-dose calcium supplementation for which there are limited data suggesting effectiveness in reducing pre-eclampsia risk[7]. Until these findings are confirmed by larger, sufficiently powered randomised trials[100,162], lower-dose supplements (500–600 mg/day) may be considered in preference to no supplementation in settings of low dietary calcium where high-dose supplementation is not feasible[7,152].

Cost-effectiveness analyses of increasing calcium intake should consider increasing dietary intake versus calcium supplementation, with consideration that many countries do not have sufficient availability of dairy products to meet dietary needs[163].

### Folate-containing multivitamin

An average of 20–30% of pregnant women have a vitamin deficiency of some kind. Without supplementation, approximately 75% of these women would show a deficit of at least one vitamin. In India, for example, about 25% of pregnant women are folate deficient[164].

Global periconceptional folic acid supplement use is low, taken by fewer than 50% of women in many countries[165]. A study of American women found that 29.7% used periconceptional folic acid supplement[166]. A study of 21,889 women in Tanzania in a geographical area with a high prevalence of anaemia found a prenatal intake of folic acid of 17.2%; notably, women were less likely to take folic acid supplements if they had pre-eclampsia/eclampsia during pregnancy (OR 0.48, 0.38–0.61)[167].

Factors associated with lower preconceptional use of folic acid are younger age, lower levels of maternal formal education, single marital status and unplanned pregnancy. In Canada, folic acid supplementation has been shown to vary according to maternal country of origin. In comparison with Canadian born women, immigrants from Northern African, Middle Eastern, Caribbean, Latin American, a South Pacific country or from China were significantly less likely to use supplements[168]. It may be that certain groups of immigrant women engage in less family planning and have more unintended pregnancies, lack knowledge regarding the benefit of folic acid supplementation, or cannot afford tablet supplements[165]. Policy makers and health practitioners can be aware of risk factors for low use and help increase folic acid supplementation in these populations.

### Exercise

Literature suggests that physical activity declines during pregnancy[169,170]. Barriers to activity during pregnancy reported by women include pregnancy symptoms, lack of time, access to child care and concerns about their safety and that of their unborn baby[171–175] and lack of advice from health professionals[176]. Conversely, significant enablers included positive psychological feelings, family influence and receiving advice from health professionals[177].

A lack of information by certain populations may contribute to low levels of exercise in pregnancy. A very recent study in a developing country found that only 36.6% of women thought that regular exercise was not harmful during pregnancy[178]. Low-income African American women report several factors that prevent them

from exercising, including a lack of information about safe types, frequency and duration of exercise. Cultural myths also exist about certain types of movements that are believed to potentially cause problems with pregnancy. For example, placing arms over their heads raised concerns that the umbilical cord would wrap around and strangulate the baby's neck[179]. This population also reports both a lack of motivation to exercise in pregnancy and a decreased level of physical activity in pregnancy[180]. Health care providers can be aware that cultural myths that may decrease exercise, and can pose questions to understand the beliefs of their patients regarding physical activity in pregnancy. It may be beneficial to provide information to help dispel misperceptions and ensure women understand the role of exercise in contributing to health pregnancy outcomes.

**Low molecular weight heparin**

If LMWH were effective for prevention of placental complications, a dalteparin study (116 women) found that the incremental cost of preventing one case of severe pre-eclampsia or a SGA infant was $54.00[181]. Further research is needed to clarify whether LMWH can be considered a cost-effective intervention in resource-constrained settings.

**Lifestyle changes**

Although no randomised trials exist on stress reduction on the incidence of pre-eclampsia, studies do suggest possible benefits for women at increased risk. Proximity to city parks has been shown to be associated with a beneficial impact on blood pressure during the first trimester of pregnancy[182]. Further research is needed to elucidate the mechanism accounting for this benefit and to determine whether the recommendation of visiting a green area is an effective and cost-effective intervention.

Yoga is a method associated with stress reduction. High-risk pregnant women in a controlled trial that were randomised into a yoga versus control group showed a significant reduction in pre-eclampsia ($p = 0.042$). Further research is needed to determine whether this is a cost-effective intervention for women[183].

**BEST PRACTICE POINTS**

(Please see Appendix 6.3 for the evaulation of the strength of recommendations and the quality of the evidence on which they are based.)

**Prevention of pre-eclampsia in women at low risk**

1. Calcium supplementation (of at least 1 g/d, orally) is recommended for women with low dietary intake of calcium (<600 mg/d, corresponding to less than two dairy servings per day).
2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, exercise for maintenance of fitness, periconceptional use of a folate-containing multivitamin for prevention of neural tube defects and smoking cessation for prevention of low birth weight and preterm birth.
3. The following may be useful: periconceptional and ongoing use of a folate-containing multivitamin or exercise.
4. The following are *not* recommended for pre-eclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursor or supplementation with magnesium or zinc.
5. The following are *not* recommended: dietary salt restriction during pregnancy, calorie restriction during pregnancy for overweight women, low-dose aspirin, vitamins C and E or thiazide diuretics.
6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, workload or stress reduction, supplementation with iron with/without folate, pyridoxine, or food rich in flavanoids.

**Prevention of pre-eclampsia in women at increased risk**

1. The following are recommended for prevention of pre-eclampsia: low-dose aspirin and calcium supplementation (of at least 1 g/d) for women with low calcium intake.
2. Low-dose aspirin (75–100 mg/d) should be administered at bedtime and initiated after diagnosis of pregnancy but before 16 weeks' gestation and may be continued until delivery.
3. Prophylactic doses of LMWH may be considered in women with previous placental complications (including pre-eclampsia) to prevent the recurrence of 'severe' or early-onset pre-eclampsia, preterm delivery, and/or SGA infants.
4. The following may be useful: L-arginine, metformin in PCOS and/or overweight women, increased rest at home in the third trimester and reduction of workload or stress.
5. The following may be useful for prevention of other pregnancy complications: prostaglandin precursors, magnesium supplementation and heparin thromboprophylaxis.
6. The following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of pre-eclampsia): abstention from alcohol, periconceptional use of a folate-containing multivitamin and smoking cessation.
7. The following are *not* recommended: calorie restriction in overweight women during pregnancy, weight maintenance in obese women during pregnancy, antihypertensive therapy specifically to prevent pre-eclampsia, vitamins C and E.
8. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet, exercise, selenium, garlic, zinc, pyridoxine, iron (with or without folate), or multivitamins with/without micronutrients all.

## WHAT INTERNATIONAL GUIDELINES SAY

A systematic review of 13 international clinical practice guidelines (CPGs) on hypertensive disorders of pregnancy[184] summarises international consensus regarding definitions for women at low and at increased risk of pre-eclampsia.

Women at low risk are recommended NOT to restrict dietary salt or take vitamins C and/or E by four guidelines[185–188] and NOT to take diuretics by three guidelines[186–188]. Only two guidelines recommend calcium supplementation (1–2 g/day)[187,188]. Only one guideline (SOGC, Society of Obstetricians and Gynaecologists of Canada) mentioned low-dose aspirin as an intervention that was NOT recommended[187]. One guideline (SOGC) reported several interventions with insufficient evidence to make a recommendation, including a heart-healthy diet, workload or stress reduction, iron supplementation with/without folate, vitamin D, pyridoxine and food rich in flavonoids[187].

Women at increased risk of pre-eclampsia are recommended to take calcium supplementation (1–2.5 g/d) if they have low calcium intake by three guidelines[187–189]. Five guidelines recommended low-dose aspirin (60–162 mg/d)[185–189] with initiation in early pregnancy[185–189], and three guidelines recommend that it continue until delivery[186,187,189]. Women at increased risk are recommended NOT to restrict dietary salt by three guidelines[185,186,188] or to take vitamins C and/or E by four guidelines[185–188].

## SUMMARY

Pre-eclampsia and its complications represent an important cause of maternal and perinatal morbidity and mortality. Optimising primary prevention efforts in the periconceptional and antenatal period are essential to reduce this burden. This chapter summarises the most current evidence-based recommendations regarding lifestyle changes and drugs that have been shown to help prevent pre-eclampsia and its complications. Health care providers should promote these recommendations to help minimise the deleterious effects of pre-eclampsia and its complications. Considerations unique to LMIC and to marginalised populations that may affect implementation of recommended interventions are also presented. Reducing the impact of pre-eclampsia in LMIC countries and marginalised populations will require health systems capacity building, strengthening of infrastructure, and implementation of interventions appropriate to low-resource settings.

## PRIORITIES FOR FUTURE RESEARCH

This chapter identifies gaps in knowledge regarding the prevention of pre-eclampsia. The effectiveness of prevention efforts relies on the dissemination of knowledge among health care providers and women with subsequent uptake of given recommendations. To help identify barriers and help achieve these objectives, there is a need for further implementation research.

Further research is also needed to elucidate the effects of the following in preventing pre-eclampsia in low-risk women: a heart-healthy diet; workload or stress reduction; supplementation with iron without or without folate; and pyridoxine or food rich in flavonoids. In women at increased risk, further investigation is required regarding the effects of the heart-healthy diet; exercise; selenium; garlic; zinc; pyridoxine; iron (with or without folate); and multivitamins with/without micronutrients.

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