European Journal of Obstetrics & Gynecology and Reproductive Biology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Primary and secondary prevention of preterm birth: a review of systematic reviews and ongoing randomized controlled trials

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ARTICLE INFO

Article history:
Received 2 December 2018
Accepted 13 December 2018
Available online xxx

Keywords:
Preterm birth
Prevention
Prematurity
Neonatal
Obstetrics

ABSTRACT

Background: Preterm birth (PTB) is a leading cause of perinatal morbidity and mortality. Interventions aimed at preventing PTB can be classified as primary, secondary, or tertiary prevention.
Objective: To conduct a review of systematic reviews on the effectiveness and safety of primary and secondary preterm birth prevention interventions.
Search strategy: A systematic literature search of the Cochrane, PubMed/Medline, EMBASE and CINAHL databases was conducted on 2 September 2015, and updated on 21 November 2016.
Selection criteria: We included any published systematic review of randomized controlled trials (RCTs) or individual patient data (IPD) of RCTs related to primary or secondary prevention of PTB, published between 2005–2016 where gestational age at birth (of any interval) was a pre-specified outcome. Individual trials and non-systematic reviews were not eligible.
Data collection and analysis: The population of interest was all pregnant women, regardless of PTB risk. The primary outcome was PTB < 37 weeks.
Main Results: In total, 112 reviews were included in this study. Overall there were 49 Cochrane and 63 non-Cochrane reviews. Eight were individual participant data (IPD) reviews. Sixty reviews assessed the effect of primary prevention interventions on risk of PTB. Positive effects were reported for lifestyle and behavioural changes (including diet and exercise); nutritional supplements (including calcium and zinc supplementation); nutritional education; screening for lower genital tract infections. Eighty-three systematic reviews were identified relating to secondary PTB prevention interventions. Positive effects were found for low dose aspirin among women at risk of preeclampsia; clindamycin for treatment of bacterial vaginosis; treatment of vaginal candidiasis; progesterone in women with prior spontaneous PTB and in those with short midtrimester cervical length; L-arginine in women at risk for preeclampsia; levothyroxine among women with tyroid disease; calcium supplementation in women at risk of hypertensive disorders; smoking cessation; cervical length screening in women with history of PTB with placement of cerclage in those with short cervix; cervical pessary in singleton gestations with short cervix; and treatment of periodontal disease.
Conclusion: The overview serves as a guide to current evidence relevant to PTB prevention. Only a few interventions have been demononstrated to be effective, including cerclage, progesterone, low dose aspirin, and lifestyle and behavioural changes. For several of the interventions evaluated, there was insufficient evidence to assess whether they were effective or not.

Contents

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https://doi.org/10.1016/j.ejogrb.2018.12.022
0301-2115/

Introduction

An estimated 11% of live births were born preterm, equating to nearly 15 million preterm babies born in 2014 [23]. Of the 38 countries with high-quality data, preterm birth rates have increased since 2000 in 26 countries. Complications of PTB were the leading cause of death in children under five years of age globally in 2016, accounting for approximately 16% of all deaths, and 35% of deaths among newborns [1]. In general, preterm-associated neonatal and child survival rates are much poorer in low- and middle-income countries [1–3].

Interventions aimed at preventing PTB can be classified as primary (i.e. directed at all women, including populations of women at higher- or –lower-risk of PTB), secondary (i.e. directed at a sub-group of women with known or identified risk factor/s), or tertiary prevention (interventions used after preterm labor (PTL) has commenced) [4]. Primary and secondary prevention includes a wide range of interventions, including pharmacological treatments, such as low-dose aspirin [5] or progesterone [6–9]; nutritional interventions [10]; surgical procedures, such as cervical cerclage [11,12]; devices, such as cervical pessary [13–15]; as well as more complex, population-level or health system-level interventions, such as dietary education and screening and treatment programmes [16].

In 2015, a review of systematic reviews on primary and secondary preterm birth (PTB) interventions was initiated with two main objectives:

1) to systematically assess existing literature regarding effectiveness and safety of interventions to prevent PTB; and 2) to prioritize interventions for further research in low- and middle-income country settings. Reviews of systematic reviews on PTB prevention have been conducted previously (2014).(16) However, these have focused only on Cochrane reviews. There is an increasing number of high-quality systematic reviews of randomized controlled trials (RCTs) on PTB prevention published in other journals. Furthermore, a number of important reviews have been published or updated in the past five years, including several individual patient data (IPD) meta-analyses.

In this paper, we present the findings of the review of systematic reviews of primary and secondary PTB prevention interventions, as well as a review of planned and ongoing RCTs.

Methods

This review of systematic reviews was conducted according to standards of the *Cochrane Handbook of Systematic Reviews of Interventions* [17], and reported according to the PRISMA Checklist [18]. The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42015 027440).

Eligibility criteria

We included any published systematic review or IPD of RCTs related to primary or secondary PTB prevention published between January 2005 to October 2016 where gestational age at birth (of any interval) was a pre-specified outcome. Individual trials and non-systematic reviews were excluded. Systematic reviews of non-randomized studies were also excluded.

We defined a systematic review as reviews that: had a clear research question, described a comprehensive literature search (including at least two databases), used a duplicated study selection and data extraction process, and described the characteristics of the included studies. The population of interest was all pregnant women, regardless of PTB risk, including women with singleton or multiple pregnancies, without clinically confirmed preterm labor (PTL). Interventions of any type, at any level of the health system (facility, health system, and health policy) were eligible. Reviews of pre-conception, tertiary prevention or postpartum/postnatal interventions were excluded. In order to maximize inclusiveness, systematic reviews of interventions that may have an indirect effect on PTB (i.e. interventions aimed at other conditions in pregnancy, but potentially also affecting PTB) were also eligible. If the review included both RCTs and non-RCTs, we included the review if results from RCTs only were reported separately. Where two or more reviews addressed the same research question, we included all reviews. However, where a systematic review had been specifically updated, we included only the most recent version.

Literature search, screening and extraction

A systematic literature search of the Cochrane, PubMed/Medline, EMBASE and CINAHL databases was conducted on 2nd September 2015, and updated on 21st November 2016. As the publications of interest are high-quality systematic reviews, grey literature sources were not included (search strategy provided in Supplementary material). All citations were downloaded into a reference manager and duplicate citations removed. Two authors independently screened titles and abstracts of each citation, and included those for full text review (according to criteria defined above). Each retrieved full text article was independently evaluated for inclusion by two authors. We developed and pre-tested a data extraction form, capturing review characteristics and outcome data for comparisons of interest. Where the GRADE criteria [19] were used for our primary outcome (i.e. PTB < 37 weeks), the certainty of evidence was extracted. Any differences during screening and extraction were resolved through discussion and/or consultation with a third author. Two authors independently also assessed the methodological quality of the included reviews using the AMSTAR tool [20].

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We also conducted a systematic search of the International Clinical Trials Registry Platform (ICTRP) on 15th November 2016. ICTRP aggregates 17 national and international trial registries (including Clinicaltrials.gov, the EU Clinical Trials Register and the Pan African Clinical Trials Registry), providing a single, regularly updated search portal for all registered trials. We used a keyword search in ICTRP (using "premature" or "preterm birth" or "prematurity") to identify any RCTs of primary or secondary PTB prevention interventions with date of registration from 1st January, 2005 to 31st December, 2016. We extracted characteristics of any eligible registered RCTs. Identified trials were reviewed independently for inclusion by two authors, and classified by type of intervention.

Outcomes

Primary and secondary outcomes were pre-defined before data extraction. Selection of outcomes was informed by findings of the COPOP project on core outcomes for PTB prevention [21]. as well as critical outcomes used in the WHO antenatal care recommendations for a positive pregnancy experience [22]. The primary outcome was PTB < 37 weeks. The secondary outcomes were PTB < 34, <32, and <28 weeks (or any other reported GA threshold), maternal satisfaction, and neonatal outcomes including low birth weight (LBW) (i.e. birth weight <2500 g), admission to neonatal intensive care unit (NICU), fetal mortality (i.e. fetal death after 20 weeks), neonatal mortality (as defined by the trials) and perinatal death (i.e. either fetal mortality or neonatal mortality).

Our review protocol pre-specified several other maternal and neonatal morbidity outcomes (Prospero registration number CRD42015027440). However, during piloting of data extraction we found the secondary outcome list to be unmanageably large. The group agreed through consensus to reduce the list, considering what data were likely to be available.

Classification, analysis and reporting

We aimed to classify all identified interventions as either primary or secondary prevention interventions, or both. Analysis and reporting was primarily descriptive, presenting the identified interventions and the magnitude of effect on primary and secondary outcomes.

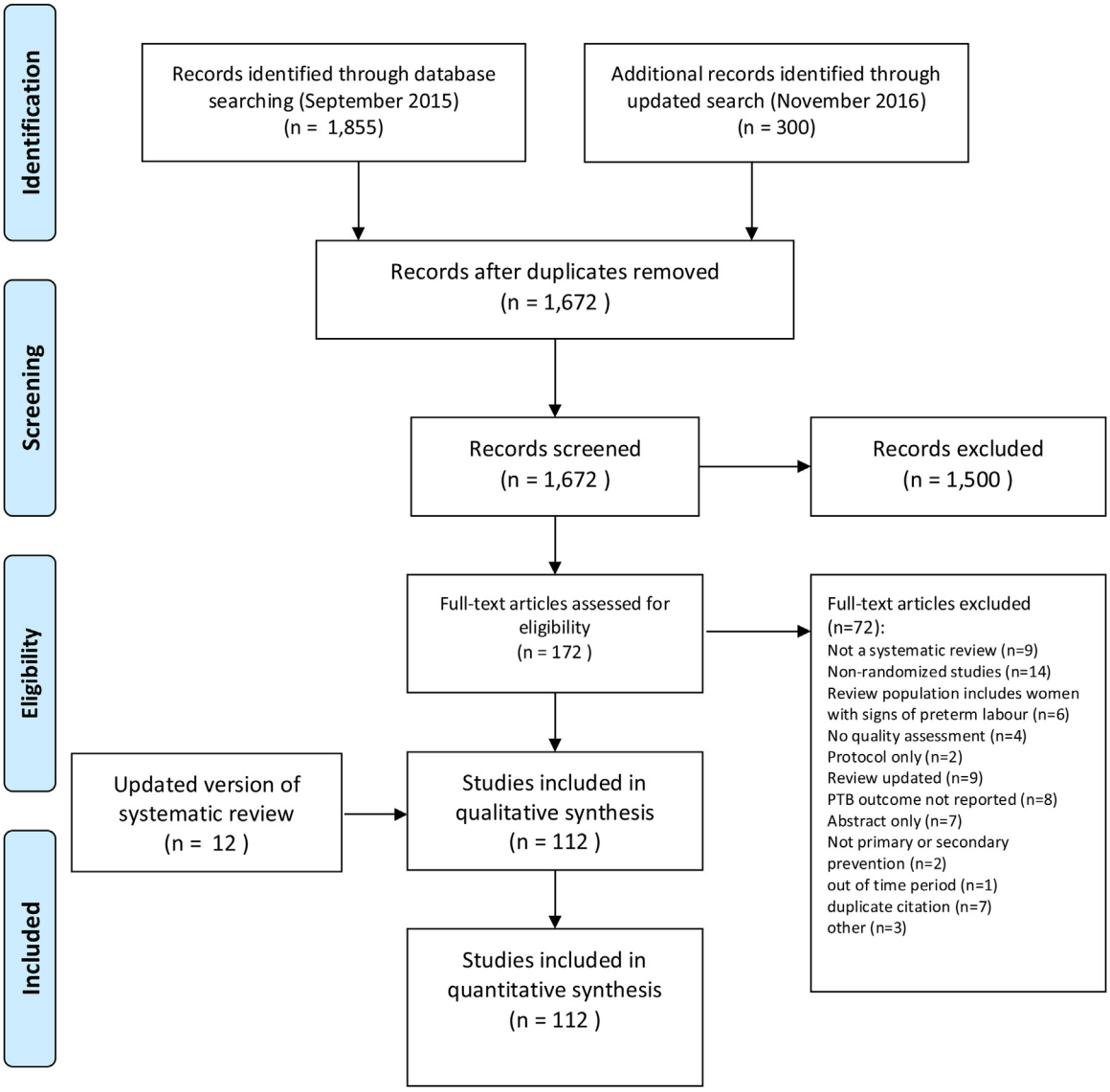

Fig. 1. Flow chart for search and identification of studies in the review of systematic reviews.

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Results

Study selection

The initial search identified 1,372 unique citations; 132 were included for full text review. An updated search was run in November 2016, which identified an additional 300 citations, yielding 40 for full text review. Of the 172 full text articles reviewed, 72 were excluded. An additional 12 papers were added, as they were the latest version of a published review. In total, 112 reviews were included (Fig. 1).

An overview of types of interventions identified is shown in Table 1. Classification of the included reviews according to types of interventions is shown in Supplementary material. Table 2 shows the results of searching the ICTRP trial database. Overall 172 registered trials were found, 47 on primary PTB prevention and 125 on secondary PTB prevention. Most of the trials evaluated the effect of different drugs, mostly aspirin and progesterone. Twenty four trials evaluated benefits of nutritional supplementation in prevention of PTB. Of them, eight were on antenatal supplementation of polyunsaturated fatty acids.

Supplementary material shows the descriptive characteristics of included systematic reviews. Overall there were 49 Cochrane and 63 non-Cochrane reviews. Eight were IPD reviews. The publication date of the trials included in the reviews ranged from 1953 to 2016. The number of included trials in each review ranged from 0 to 86. Only 38 reviews used the GRADE criteria. Figs. 2 and 3 show the effect estimates of primary (Fig. 2) and secondary (Fig. 3) prevention intervention on PTB < 37 weeks.

Intervention effects on primary outcome (preterm birth<37 weeks)

I **Primary prevention of preterm birth**

Sixty reviews assessed the effect of primary prevention strategies on risk of PTB (Fig. 2). For many interventions, there were multiple, overlapping systematic reviews.

1 *Medications*: Thinkhamrop (2015) compared use of antenatal prophylactic antibiotics with placebo among women (lowor high risk of PTB) (5 trials, 1480 women) and showed no effect on risk of PTB (RR 0.85, 95% CI 0.64–1.14).

2 *Models of care:* Two reviews evaluated models of health care. Catling et al. (2015) conducted a Cochrane review of four trials and 2350 women enrolled in group antenatal care compared to standard care. There was a marginal difference in risk of PTB (RR 0.75, 95% CI 0.57–1.00, moderate-quality evidence). Fernandez Turienzo et al. (2016) meta-analysed 15 trials of 22,437 women randomized to alternate models of antenatal care (compared to standard care). This included "midwife-led continuity models of care, PTB prevention programmes, clinic-based specialised care and stand-alone interventions involving the provision of health or social care delivered in conjunction with standard antenatal care". They found a statistically significant decrease in risk of PTB < 37 weeks in women receiving alternate models of care (RR 0.84, 95% CI 0.74–0.96). The authors identified significant heterogeneity among trials.

3 *Lifestyle and behavioural changes:* Diet and/or interventions targeted at increasing physical activity were evaluated in four reviews. Bain et al. (2015) compared diet and exercise advice with no advice in an unselected group of pregnant women (5 trials, 2,713 women). Their primary interest was prevention of excessive weight gain in pregnancy. The risk of PTB was reduced among women enrolled in diet and exercise (RR 0.71, 95% CI 0.55–0.93). This finding was not replicated in other systematic reviews, although intervention definitions were somewhat different.

Benja et al. (2015) conducted a Cochrane review on the effect of diet and exercise advice compared to no advice in an unselected group of women in preventing gestational diabetes mellitus (GDM) (16 trials, 5923 women). They found no difference in risk of PTB (RR 0.91, 95% CI 0.68–1.22), however eligible studies were those that related to addressing GDM risk as opposed to gestational weight gain.

Thangaratinam et al. (2012) compared any dietary or lifestyle intervention to standard care among a group of unselected pregnant women, including women with GDM or obesity. They identified no effects on PTB risk (13 trials, 2652 women, RR 0.78, 95% CI 0.60–1.02), nor when stratified based on intervention (dietary advice, physical activity, or both).

Table 1
Overview of types of interventions identified.

	Primary prevention	Secondary prevention
Drug	Antiplatelet	Antiplatelet
	Antibiotics	Antibiotics
		Progestogens
		Other
Device	–	Pessary
Psychosocial	Telephone support	Support for smoking cessation
Surgical/procedural	–	Cerclage
		Dental treatment
		Mode of delivery
Nutritional supplementation or treatment	Calcium	Iron +/- folic acid
	Iron +/- folic acid	Polyunsaturated fatty acids
	Polyunsaturated fatty acids	Vitamins (A)
	Vitamins (A,B6,B12,C,D,E)	Other
	Zinc	
	Multiple micronutrients	
	Antioxidants	
	Probiotics	
	Other	
Lifestyle or behavioural	Diet	Bed rest
	Exercise	Activity restriction
Screening +/- treatment (use of investigations, examinations or special tests, which may or may not prompt the use of certain interventions)	Screening whole population	Screening a selected sub-group only
Health system	Alternative model of care	–

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Table 2
Results of searching ICTRP trial database (N = 172).

	Primary prevention (N = 47)	Secondary prevention (n = 125)
Drug (n = 71)	Antiplatelet - 1 Antibiotics – 1 Other – 1	Antiplatelet - 2 Antibiotics - 7 Progestogens - 51 Other – 8
Device (n = 21)		Pessary – 21
Psychosocial (n = 1)	1	0
Surgical/procedural (n = 15)	0	Cerclage - 11 Dental treatment - 1 Mode of delivery - 3
Nutritional supplementation or treatment (n = 24)	Iron +/- folic acid - 1 Polyunsaturated fatty acids - 7 Vitamins - 3 Multiple micronutrients - 3 Probiotics - 3 Other – 3	Polyunsaturated fatty acids - 1 Zinc - 1 Probiotics - 2
Lifestyle or behavioural (n = 8)	6	2
Screening +/- treatment (n = 14)	9	5
Health system (n = 6)	5	1
Multiple (n = 12)	3	9

Kramer and McDonald (2009) evaluated the effects of increased exercise in sedentary women and decreased exercise in fit women (they did not include dietary interventions). There was no effect on PTB with increased exercise among sedentary women (3 trials, 111 women, RR 1.82, 95% CI 0.35–9.57) or with reduction in exercise among physically fit women (1 trial, 61 women, RR 1.18, 95% CI 0.08–17.99).

4 *Nutritional supplementation:* Nutritional supplementation interventions were evaluated in 34 systematic reviews. Calcium supplementation was evaluated in five reviews. Calcium of any dose was evaluated by Imdad et al. (2011) in a

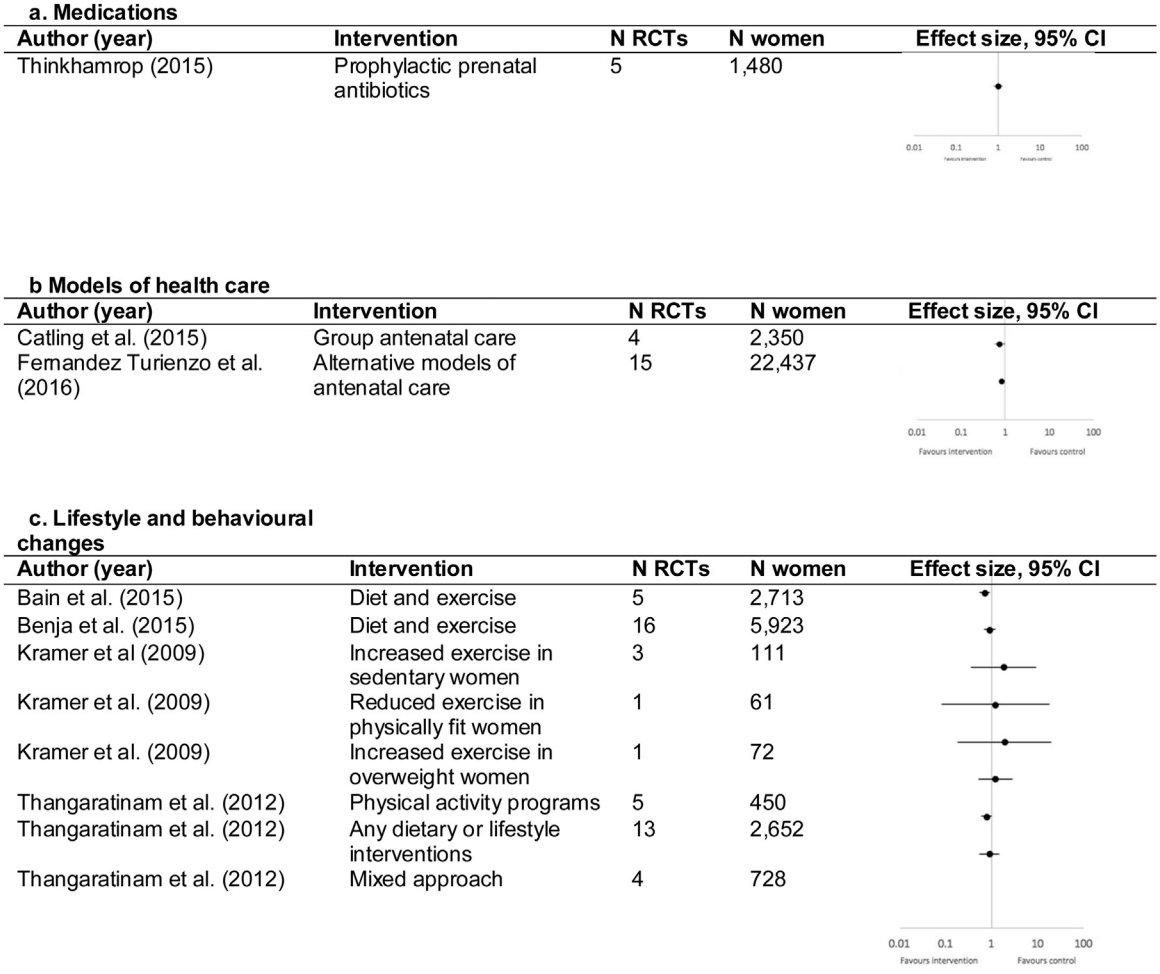

Fig. 2. Effect estimates of primary prevention intervention on preterm birth.

d. Nutritional supplementation

Author (year)	Intervention	N RCTs	N women
Thangaratinam et al. (2012)	Dietary advice	4	1474
Ota et al. (2015b)	Specific nutritional education	2	449
Rumbold et al. (2008)	Antioxidants	5	5,198
Ota et al. (2015b)	High protein supplementation	1	505
Ota et al. (2015b)	Balanced protein and energy supplementation	0	0
Ota et al. (2015b)	Isocaloric balanced protein supplementation	0	0
Al Dorazi et al. (2014)	Calcium	4	10,129
Imdad (2011)	Calcium	5	9,919
Buppasiri et al. (2015)	Calcium (<1000mg/d)	1	660
Buppasiri et al. (2015)	Calcium (>!000mg/d)	12	15,479
Hofmeyr et al., (2014)	Calcium (≥ 1000mg/day)	11	15,275
Buppasiri et al. (2015)	Calcium (any dose)	13	16,139
Saccone et al. (2016)	Folic acid	1	1,654
Lassi Zohra et al. (2013)	Folic acid alone or with other supplements	3	2,959
Pena-Rosas et al. (2015a)	Iron (daily)	13	19,286
Cantor et al. (2015)	Iron	2	1,010
Pena-Rosas et al. (2015b)	Iron (intermittent, oral) +/- other supplements	5	1,177
Haider et al., (2013b)	Iron only	10	not specified
Haider et al., (2013a)	Iron±folic acid	12	not specified
Salvig et al. (2011)	Long-chain n-3 fatty	4	1,187
Makrides et al. (2016)	Marine oil or other prostaglandin precursor	5	1,916
Suchdev et al., (2015)	Micronutrient powders for point-of-use fortification of semi-solid foods including iron and other micrnonutrients (≧3)	0	0
Ramakrishnan et al. (2012)	Multiple micronutrient (≥ 5)	9	45,909
Fall et al. (2009)	Multiple micronutrients	12	not specified
Haider et al. (2015)	Multiple micronutrients (3 or more micronutrients) *	1	not specified
Haider et al. (2015)	Multiple micronutrients with iron and folic acid*	15	not specified
Saccone et al. (2016)	Omega-3	9	3,854
Kar et al. (2016)	Omega-3	9	5,980
Saccone et al. (2015)	Omega-3 supplementation	7	3,854
Chen et al. (2016)	Fish oil	14	1,057
Othman et al. (2007)	Probiotics to treat and/or prevent urogenital infections	1	238
Salam Rehana et al. (2015)	Pyridoxine	0	0
McCauley et al. (2015)	Vitamin A	5	40,137
Thorne-Lyman et al. (2012)	Vitamin A	7	19,799
Thorne-Lyman et al. (2012)	Vitamin D	2	529
Pérez-López et al. (2015)	vitamin D +/- Calcium and other vitamins	3	384
De-Regil et al. (2012)	Vitamin D +/- Calcium supplementation	6	1,023
Rumbold et al., (2015)	Vitamin E +/- Other supplements	11	20,565
Dror et al. (2012)	Vitamins B6, B12 or C	9	19,631
Chaffee et al. (2012)	Zinc	16	7,818
Ota et al. (2015a)	Zinc	16	7,637

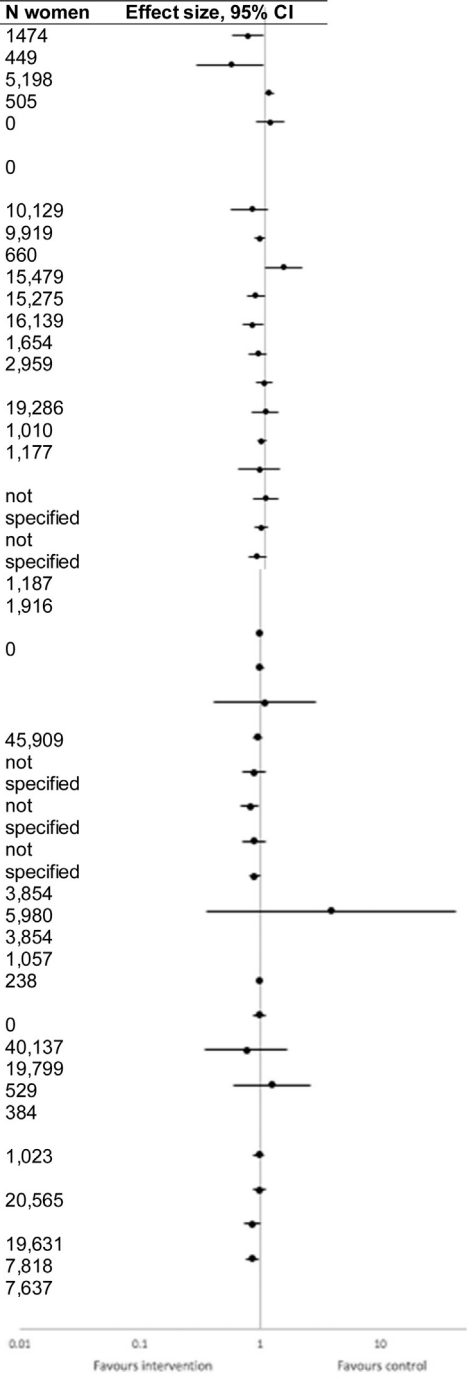

Fig. 2. (Continued)

review of the role of calcium in reducing risk of hypertensive disorders of pregnancy (5 trials, 9919 women). Calcium (of any dose) initiated prior to 32 weeks gestation was found to reduce risk of PTB (RR 0.88, 95% CI 0.78–0.99) when compared to placebo or no supplementation. Hofmeyr et al. (2014) also evaluated the effects of calcium supplementation for prevention of hypertensive disorders (11 trials, 15,275 women), and showed a decrease in PTB risk with high dose calcium >1 g/day administered to all pregnant women (RR 0.76, 95% CI 0.60 to 0.97, high-quality evidence).

The Cochrane review by Buppasiri et al. (2015) evaluated the role of calcium supplementation in improving obstetrical outcomes other than hypertensive disorders. The risk of PTB was not reduced with calcium supplementation compared to placebo or no supplementation, (13 trials, 16139 women RR 0.86, 95% CI 0.70–1.05). However, high dose (>1 g/day) but not low dose (<1 g/day) calcium supplementation was associated with a reduction in risk of PTB (RR 0.81, 95% CI 0.66 to 0.99). Iron supplementation was evaluated in four reviews. Daily iron supplementation with iron alone or in combination with folic acid or other minerals or vitamins was found to reduce PTB < 34 weeks when compared to placebo, no treatment, or an equivalent non-iron supplement (RR 0.51, 95% CI 0.29 to 0.91), but the risk of PTB < 37 weeks was not significantly

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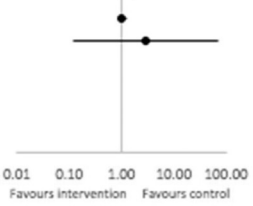
e. Psychosocial interventions

Author (year)	Intervention	N RCTs	N women	Effect size, 95% CI
Dennis et al. (2008)	Telephone support by lay person or health professional	14	8,037	

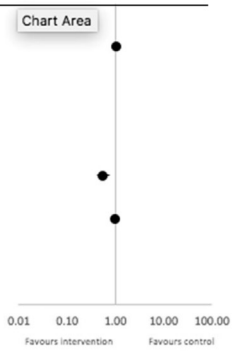
g. Special tests or investigations

Author (year)	Intervention	N RCTs	N women	Effect size, 95% CI
Alfirevic et al. (2015)	Doppler	4	12,162	
Heazell et al. (2015)	Tests of placental function	1	118	



f. Screening with or without treatment

Author (year)	Intervention	N RCTs	N women	Effect size, 95% CI
Alexander et al. (2010)	Repeat digital cervical examinations throughout pregnancy	2	7,163	
Davey et al. (2013)	PTB risk scoring, and subsequent interventions	0	0	
Nygren et al. (2008)*	Screening for bacterial vaginosis	0	0	
Sangkomkamhang et al. (2015)	Antenatal lower genital tract infection screening +/- treatment	1	4,155	
Spencer et al. (2015)	Universal screening for thyroid dysfunction	1	4,516	



*Results for treatment of bacterial vaginosis in low and average risk women is reported as absolute risk reduction and not included in this table

Fig. 2. (Continued)

reduced (13 trials, 19, 286 women, RR 0.93, 95% CI 0.84–1.03) (Pena Rosa et al., 2015a). In a separate review assessing intermittent iron supplementation, the risk of PTB < 37 weeks or <34 weeks was not reduced (Pena Rosa et al., 2015b).

Haider et al., (2013) identified 12 trials (unspecified number of women) that evaluated the effect on PTB < 37 weeks with iron supplementation, alone or in combination with folic acid. There was no significant effect on PTB (RR 0.84, 95% CI 0.68–1.03). Cantor et al. (2015), using a different timeframe and different databases, compared routine iron supplementation to an unspecificed placebo. They identified two trials (1010 women) and no significant effect on PTB (RR 0.88, 95% CI 0.55–1.42).

Folic acid supplementation was evaluated in two reviews. Saccone and Berghella (2016) compared folic acid supplementation to placebo or no treatment and identified one trial (1654 women). In this trial, there was no significant effect on PTB (RR 0.99, 95% CI 0.82–1.18). Lassi Zohra et al. (2013) evaluated folic acid with or without other supplements compared to placebo or non-folate supplements. They identified three trials (2959 women), and no effect on PTB (RR 1.01, 95% CI 0.73–1.38).

Vitamin A supplementation was evaluated in two reviews. Both compared vitamin A supplementation to placebo. McCauley et al. (2015) conducted a Cochrane review on the effects of Vitamin A on obstetrical outcomes. They compared vitamin A alone versus placebo (4 trials, 40137 women, RR 0.98, 95% CI 0.94–1.01), vitamin A versus a multivitamin lacking vitamin A (0 trials), and a vitamin A containing multivitamin versus a multivitamin without (1 trial, 136 women, RR 0.39, 95% CI 0.08–1.93, high quality evidence).Thorne-Lyman & Fawzi (2012b) was a non-Cochrane review that compared vitamin A alone versus placebo (7 trials, 19799 women) and found no effect on PTB risk (RR 0.99, 95% CI 0.88–1.10).

Vitamin D supplementation, alone or in conjunction with other supplements, was evaluated in three reviews, and none showed significance in terms of risk of PTB Thorne-Lyman & Fawzi (2012a) evaluated vitamin D supplementation at any dose, compared to placebo, among low risk women (2 trials, 529 women). There was no effect on PTB (RR 0.77, 95% CI 0.35–1.66). Pérez-López et al. (2015) compared vitamin D, alone or in combination with calcium and vitamin supplements, to placebo, no supplement, or supplements without vitamin D (3 trials, 384 women) and also found no effect on PTB (RR 1.26, 95% CI 0.60–2.63). De-Regil et al. (2012) also evaluated vitamin D (at any dose) alone or in combination with another supplement, compared to placebo or no supplements. They identified 6 trials (1023 women) but

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a. Devices

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Urquhart et al. (2015)	Home uterine activity monitoring	8	4,834	

b. Lifestyle and Behavioural Changes

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Sosa et al. (2015)	Prescription of bed rest in hospital or at home	1	1,266	
Crowther et al. (2010)	Hospitalization and bed rest during antenatal period	8	not specified	

c. Antiplatelet agents

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Askie et al. (2007)	ASA +/- dipyridamole	26	31,316	
Meher et al. (2016)	Antiplatelet agents	0	0	
Xu et al. (2015)	LDASA	29	21,403	
Cristina et al. (2009)	LDASA +/- Vitamin C/E	6	9,966	
Roberge et al. (2013)	LDASA +/- dipyridamole	22	11,302	
Roberge et al. (2012)	LDASA +/- dipyridamole	5	556	
Yao et al. (2015)	LDASA	5	860	
Henderson et al. (2014)	LDASA	10	11,779	
van Vliet et al. (2017)	LDASA/dipyridamole	17	28,797	
Areia et al. (2016)	LMWH and ASA	not specified	not specified	
Khanprakob et al. (2012)	COX inhibitor (rofecoxib)	1	98	

d. Antibiotics

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Kenyon et al.(2013)	Antibiotics for PPROM	3	4,931	
Okun et al. (2005)	Antibiotics for BV or Trichomoniasis	11	6,052	
Lamont et al. (2011)	Clindamycin for BV	5	2,346	
Brocklehurst et al. (2013)	Treatment for BV	13	6,491	
Nygren et al. (2008)	Treatment for bacterial vaginosis	6	1,305	
Gülmezoglu et al. (2011)	Metronidazole for Trichomoniasis	1	604	
Roberts et al. (2015)	Treatment of vaginal candidiasis	2	685	
Schneeberger et al. (2015)	Nitrofurantion antibiotic prophylaxis and close surveillance for recurrent UTI	1	147	
Thinkhamrop et al. (2015)	Prophylactic prenatal antibiotics (excluding intrapartum antibiotics) in women with previous PTB and current BV	1	258	
Thinkhamrop et al. (2015)	Prophylactic prenatal antibiotics (excluding intrapartum antibiotics) in women with previous PTB and no BV	2	500	
Thinkhamrop et al. (2015)	Prophylactic prenatal antibiotics (excluding intrapartum antibiotics) in high risk women	2	758	

Fig. 3. Effect estimates of secondary prevention intervention on preterm birth.

none included preterm birth as an outcome. In their update (De-Regil et al., 2016) three trials (477 women) compared vitamin D alone compared to placebo. There was an overall decreased risk of PTB (RR 0.36, 95% CI 0.14-0.93). Interestingly, women who received vitamin D with calcium had an increased risk of PTB compared to women who received no supplementation or placebo (3 trials, 798 women, RR 1.57, 95% CI 1.01–2.43). The authors noted that the risk of bias in most trials is unclear and many trials were at high risk of bias for blinding at attrition rates.

Vitamin E supplementation was not shown to reduce PTB risk in one review (Rumbold et al., 2015; 11 trials, 20565 women, RR 0.98, 95% CI 0.88–1.09).

Salam Rehana et al. (2015) aimed to evaluate the effect of pyridoxine on PTB and did not find any trials that met inclusion criteria.

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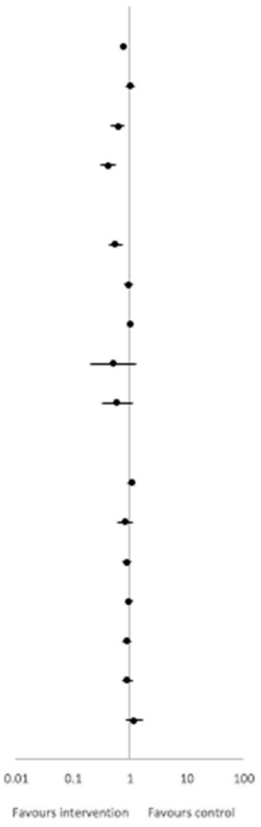
e. Progesterone

Author (year)	Intervention	N trials	N women
Likis et al.(2012)	Progesterone (any) in women with prior PTB	5	372
Likis et al.(2012)	Progesterone (any) in multiple gestations	4	not specified
Likis et al.(2012)	Progesterone (any) in women with PTL	5	not specified
Coomarasamy et al. (2006)	Progesterone (any)	8	not specified
Dodd et al. (2013)	Progesterone (any) for high risk women	0	0
Dodd et al. (2013)	Progesterone (any) for women with previous PTB	10	1,750
Dodd et al. (2013)	Progesterone (any) for women with short cervix	3	1,303
Dodd et al. (2013)	Progesterone (any) for multiple pregnancies	8	2,674
Dodd et al. (2013)	Progesterone (any) for singletons with threatened preterm labour	2	223
Dodd et al. (2013)	Progesterone (any) for women with other risk factors for PTB	3	482
Sotiriadis et al. (2012)	Progesterone (any)	16	not specified
Schuit et al. (2015)	Progesterone - IM	6	2,021
Conde-Agudelo et al. (2013)	Progesterone - vaginal	4	158
Romero et al. (2012)	Progesterone - vaginal	5	775
Schuit et al. (2015)	Progesterone - vaginal	7	929
Romero et al. (2016)	Progesterone - vaginal	4	723
Saccone et al. (2016)	Progesterone - vaginal (compared to IM)	3	680
Conde-Agudelo et al. (2013)	Progesterone - vaginal (compared to cerclage)	not specified	not specified

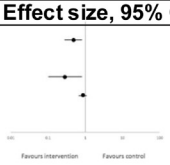
Effect size, 95% CI



f. Other medications

Author (year)	Intervention	N trials	N women
Domiak-Wall et al. (2014)	L-arginine	1	672
Domiak-Wall et al. (2014)*	L-Arginine ± any other agent	7	884
Reid et al. (2013)	Levothyroxine	1	115
Yamasmit et al. (2015)	Oral betamimetics	4	276

Effect size, 95% CI



*ES not specified

g. Models of health care

Author (year)	Intervention	N trials	N women
Whitworth et al. (2011)	Specialized antenatal clinic care	3	3,400
Dodd et al. (2015)	Specialized antenatal care	0	0

Effect size, 95% CI

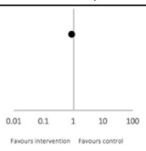


Fig. 3. (Continued)

Two reviews addressed zinc supplementation in pregnancy. Chaffee and King (2012) compared zinc supplementation to placebo/no intervention (16 trials, 7818 women) and showed a reduction in PTB (RR 0.86, 95% CI 0.75 to 0.99, low-quality evidence). Ota et al. (2015a) compared zinc supplementation to placebo or no intervention or non-zinc intervention and also showed a reduction in PTB based on 16 trials including 7637 women (RR 0.86, 95% CI 0.76 to 0.97, moderate-quality evidence).

Fish oil, marine oil, and omega-3 fatty acids was evaluated in six reviews. Kar et al. (2016) compared omega-3 fatty acid supplementation with an unspecified control group in 9 trials and 5980 women and found a reduction in PTB (RR 0.83, 95% CI 0.70 to 0.98). Salvig and Lamont (2011) evaluated long chain n-3 fatty acid supplementation compared to placebo or no supplementation (4 trials, 1187 women) and also found a reduction in PTB (RR 0.61, 95% CI 0.40 to 0.93). The remaining four reviews did not show a statistically significant effect on PTB risk but Chen et al. (2016) found a reduction in PTB < 34 weeks (RR 0.78, 95% CI 0.64 to 0.95) with fish oil supplementation.

Dietary supplementation with multiple micronutrients was evaluated in four reviews. Suchdev et al. (2015) evaluated micronutrients in powder forms for fortification of foods compared to a wide range of controls (no intervention, placebo, iron and folate supplements, iron alone, folate alone, or other

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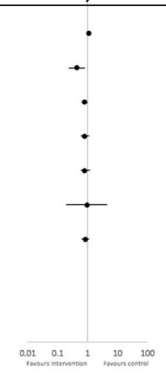
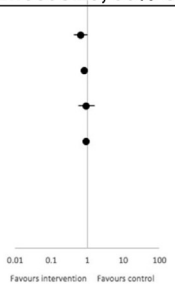
h. Nutritional supplements

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Rumbold et al. (2008)	Antioxidants	3	3,131	
Hofmeyr et al. (2015)	Calcium (≥ 1000mg/day) for women at high risk of HDP	4	568	
Hofmeyr et al. (2015)	Calcium (≥ 1000mg/day) for women with low intake	7	10,242	
Horvath et al. (2007)	LC PUFA	4	523	
Saccone et al. (2015a)	Omega-3	2	1,080	
Reid et al. (2013)	Selenium	1	169	
Wiysonge et al. (2011)	Vitamin A	3	2,110	



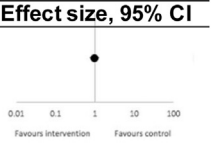
i. Psychosocial interventions

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Sukhato et al. (2015)	Any psychosocial intervention	4	684	
Chamberlain et al. (2013)	Psychosocial interventions for smoking cessation or relapse prevention	0	7,852	
Khianman et al.(2012)	Relaxation therapy for women in PTL	1	120	
Hodnett et al. (2010)	Social support	17	12,264	



j. Screening with or without treatment

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Berghella et al. (2011a)	Cervical length screening with or without cerclage	4	467	



k. Cerclage and Pessary

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Jorgensen et al. (2007)*	Cerclage	7	2,091	
Rafael et al. (2014)	Cerclage	5	128	
Liu et al. (2013)	Cerclage ± tocolysis	5	310	
Alfirevic et al. (2012)	Cerclage	9	2,898	
Berghella et al. (2011b)	Cerclage	5	874	
Conde-Agudelo et al. (2013)	Cerclage	5	504	
Alfirevic et al. (2012)	Cerclage	1	79	
Berghella et al. (2010)	Cerclage	4	552	
Alfirevic et al. (2012)	Different cerclage protocols	1	97	
Abdel-Aleem et al. (2013)	Cervical pessary	1	385	

*Effect size not statistically significant, but statistics not shown

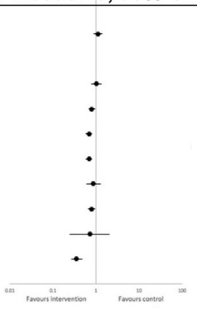


Fig. 3. (Continued)

multiple micronutrients). They identified 6 trials but none reported on their outcomes of interest, including preterm birth. Haider and Bhutta (2015), compared 3 or more micronutrients including iron and folic acid compared to placebo or no supplementation (1 trial, unspecified number of women), and compared to iron with or without folic acid (15 trials, unspecified number of women). Neither comparison showed a significant effect on PTB. Two non-Cochrane reviews were identified. Ramakrishnan et al. (2012) found no effect on preterm birth with supplementation with 5 or more micronutrients compared to 3 or less micronutrients including iron and folic acid (9 trials, 45909 women, RR 0.99, 95% CI 0.96–1.03), while Fall et al., (2009) compared "multiple micronutrients" to an unspecified placebo and also found a nonsignificant effect on PTB (12 trials, unspecified number of women, RR 1.00, 95% CI 0.93–1.09).

Nutritional education compared to no nutritional education or a different form of consultation was assessed in one systematic review (Ota et al., 2015b). This included two trials and 449 women. Risk of PTB was lower in women who received nutrional education (RR 0.46, 95% CI 0.21–0.98, low quality evidence). The same review also evaluated high

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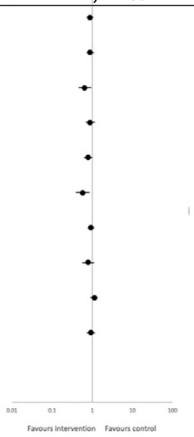
l. Treatment of Periodontal Disease

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Boutin et al. (2013)	Periodontal treatment	12	7,018	
Chambrone et al. (2011)	SRP +/- antibiotics	11	5,752	
George et al. (2011)	Periodontal treatment with scaling and/or root planning and/or oral hygiene education	10	5,496	
Rosa et al. (2012)	SRP	13	6,988	
Kim et al. (2012)	SRP	11	5,655	
Uppal et al. (2010)	SRP with polishing	10	6,142	
Polyzos et al. (2010)	SRP	11	6,558	
Schwendicke et al. (2015)	SRP and antibiotics in women with high occurrence	5	not specified	
Schwendicke et al. (2015)	SRP and antibiotics in women with moderate occurrence	8	not specified	
Fogacci et al. (2011)	Treatment of destructive periodontal disease or periodontitis	8	5,270	

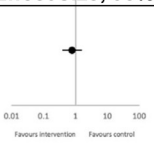


m. Other procedures

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Buchanan et al. (2010)	Planned delivery in women with PPROM	0	0	0

n. Combined approach

Author (year)	Intervention	N trials	N women	Effect size, 95% CI
Coleman (2011)	NRP and behavioural support, CBT or brief advice	3	610	



Legend

ASA aspirin
BV bacterial vaginosis
CBT cognitive behavioural therapy
LDASA low dose aspirin
LC-PUFA long chain polyunsaturated fatty acids
LMWH low molecular weight heparin
NRP nicotine replacement patch
PPROM preterm prelabour rupture of membranes
PTB preterm birth
PTL preterm labour
SRP scaling and root planning

Fig. 3. (Continued)

protein diet compared to low or no protein supplementation during pregnancy and found no effect on PTB. There was insufficient data for comparisons involving balanced protein-energy intake and isocaloric protein supplementation. Dietary advice was also evaluated by Thangaratinam et al. (2012). Compared to standard care, dietary advice was associated with a reduced risk of PTB (4 trials, 1474 women, RR 0.68, 95% CI 0.48–0.96).

Probiotics were evaluated in one review by Othman et al. (2007). Routine probiotics to prevent or treat urogenital infections in all pregnant women did not show an effect on PTB risk (1 trial, 238 women, RR 3.95, 95% CI 0.36–42.91).

5 *Psychosocial interventions:* One review (Dennis & Kingston, 2008) compared telephone support by a lay person or health care professional with no intervention and found no effect on PTB (14 trials, 8037 women, RR 0.87, 95% CI 0.75–1.01).

6 *Screening with and without treatment:* Repeat digital cervical examinations (Alexander et al., 2010; 2 trials, 7163 women) and universal screening for thyroid disease (Spencer et al., 2015; 1 trial, 4516 women) were shown to have no effect on PTB. Two reviews set out to evaluate universal screening for bacterial vaginosis (Nygren et al., 2008) and PTB scoring systems (Davey et al., 2013) but they found no eligble studies. Sangkomkamhang et al. (2015) evaluated routine screening for lower genital tract infections in pregnancy by wet mount, gram stain or vaginal culture compared to routine antenatal care without screening. They included a single trial (4155 women) and found a reduction in PTB (RR 0.55, 95% CI 0.41 to 0.75, moderate quality evidence).

7 *Special tests or investigations:* Two reviews evaluated antenatal care with routine Doppler sonography (Alfirevic et al., 2015; 4 trials, 12162 women), or routine tests of placental function with results available to clinician (Heazell et al., 2015; 1 trial, 118 women) and found no effect on PTB risk.

II **Secondary outcomes–primary preterm birth prevention**: Secondary outcomes were infrequently reported. The most commonly reported were perinatal, fetal and neonatal mortality.

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Perinatal, fetal or neonatal mortality were not significantly different with the following primary prevention interventions: omega 3 (Kar et al., 2016; Saccone & Berghella, 2015), marine oil (Makrides et al., 2006), vitamin D (De-Regil et al., 2012), vitamin A (McCauley et al., 2015; Thorne-Lyman & Fawzi, 2012), vitamins B or C (Dror et al., 2012), vitamin E (Rumbold et al., 2012), antioxidants (Rumbold et al., 2008), zinc (Ota et al., 2015a), iron supplementation (Cantor et al., 2015), group antenatal care (Catling et al., 2015), aerobic exercise (Kramer et al., 2009), folic acid supplementation (Lassi Zohra et al., 2013), nutritional education and supplementation for energy or protein (Ota et al., 2015b) or multiple vitamins and minerals (Pena-Rosas et al., 2015; Ramakrishnan et al., 2012), and routine antibiotic prophylaxis (Thinkhamrop et al., 2015).When multiple micronutrients with iron and folic acid were compared to folic acid and iron alone there was a reduction in fetal mortality with a RR 0.91, 95% CI 0.85–0.98, but there was no difference when the control group included placebo or no treatment (Haider et al., 2015). Routine calcium supplementation did not affect mortality in three reviews (Buppasiri et al., 2015; Hofmeyr et al., 2014; Al Dorazi et al., 2014), however one (Imdad, 2011) found a reduction in neonatal mortality (RR 0.70, 95% CI 0.56 to 0.88). One review of routine Doppler sonography found reduced neonatal mortality (Alfirevic et al., 2015; RR 0.34, 95% CI 0.12–0.95).

The other secondary outcomes were assessed in few reviews, and where they were reported they were largely not different. Low birth weight was reduced with certain micronutrients supplementation (Haider et al., 2015), screening and treatment for lower genital tract infections (Sangkomkamhang et al., 2015), vitamin D (Thorne-Lyman et al., 2012), and fish oil supplements (Chen et al., 2012).

Maternal outcomes were very infrequently reported. Maternal satisfaction was reported in only three reviews. Women in group antenatal care were more satisfied than women receiving conventional care (Catling et al., 2015). There was a significant reduction in maternal deaths and ICU admissions with calcium supplemtation in women regardless of risk factors and in women with low intake (Hofmeyr et al., 2014). Calcium supplementation in all pregnant women was also found to reduce maternal death in another review (Imdad, 2011).

The findings of the individual reviews are shown in Supplementary material.

III **Secondary prevention of preterm birth**

There were 83 systematic reviews of secondary prevention strategies (Fig. 3).

1 *Devices:* Urquhart et al. (2015) compared home monitoring activity versus standard care among women considered to be at risk of PTB. The risk of PTB was not statistically different between the two groups (8 trials, 4834 women, RR0.85, 95% CI 0.72–1.01). Sealing procedures for women with premature rupture of membranes was shown to reduce PTB (2 trials, 124 women, RR 0.48, 95% CI 0.38 to 0.68) in one review (Crowley et al., 2016) however the number of participants was small.

2 *Lifestyle and behavioural changes*: Two reviews evaluated bed rest at home or in the hospital for women at high risk of PTB and found no significant effect. (Sosa et al., 2015; 1 trial, 1266 women; and Crowther et al. 2010; 7 trials, 713 women).

3 *Anticoagulant and antiplatelets agents*: Eleven reviews evaluated the effect of aspirin, other COX inhibitors or heparin. One review (Meher et al., 2016) was an IPD meta-analysis on the effects of using one or more antiplatelet agents (low dose aspirin or another agent) to prevent preeclampsia. They did not report on PTB < 37 weeks, however reported on a reduction in PTB < 34 weeks (26 trials, 31272 women, RR 0.90, 95% CI 0.83 to 0.98). However, subgroup analyses of women randomized to start antiplatelets before 16 weeks gestation (19 trials, 9155 women, RR 0.90, 95% CI 0.88–1.04) or after 16 weeks (25 trials, 22117 women, RR 0.82, 95% CI 0.82–1.00) showed no statistically significant effect on PTB.

Low dose aspirin (LDASA) alone or in combination with dipyridamole was found to reduce risk of PTB among women at risk for preeclampsia in eight systematic reviews. Askie et al. (2007) was an IPD meta-analysis that compared LDASA with or without dipyridamole to placebo or no treatment among women at risk of preeclampsia (26 trials, 31316 women). There was a reduction in risk of PTB < 37 weeks (RR 0.93, 95% CI 0.89-0.98) and <34 weeks (RR 0.90, 95% CI 0.83-0.98), but not <28 weeks (RR 0.87, 95% CI 0.75–1.02). They did not assess antiplatelets given at a specific gestational, however 59% of women were randomized and received therapy at < = 20 weeks gestation. A subsequent subgroup analysis of this IPD by van Vliet et al. (2017) showed a similar trend in risk reduction of spontaneous PTB < 37 weeks (17 trials, 28797 women, RR 0.93, 95% CI 0.86-0.996), PTB < 34 weeks (RR 0.86, 95% CI 0.76–0.99). The risk of PTB < 28 weeks was not significantly reduced (RR 0.81, 95% CI 0.59–1.12).

Roberge et al. (2012) evaluated the administration of LDASA with or without dipyridamole at 16 weeks gestation or less, compared to placebo or no treatment and identified a decreased risk of PTB < 37 weeks (5 trials, 556 women, RR 0.11, 95% CI 0.04–0.33). Roberge et al., (2013) compared administration of LDASA +/- dipyridamole before or after 16 weeks gestation. There was an overall reduction in risk of PTB (22 trials, 11302 women, RR 0.81, 95% CI 0.71-0.92), but there was a greater reduction with administration at or before 16 weeks (6 trials, 904 women, RR 0.35, 95% CI 0.22–0.57) compared to after 16 weeks (16 trials, 10398 women, RR 0.90, 95% CI 0.83–0.97).

Cristina Rossi et al., (2009) observed a reduction in PTB with LDASA alone compared to placebo administered to women at high risk for pre-eclampsia (6 studies, 9966 women, OR 0.85, 95% CI 0.77–0.94). These findings were supported by subsequent reviews (Henderson et al., 2014; 10 studies, 11779 women, RR 0.86, 95% CI 0.76–0.98; Xu et al., 2015; 29 trials, 21403 women, OR 0.81, 95% CI 0.75–0.88; and Yao et al., 2015; 5 trials, 860 women with treatment started prior to 16 weeks gestation, RR 0.20, 95% CI 0.08–0.48). Of note, Cristina Rossi et al., (2009) also assessed vitamin C and E versus placebo in reducing PTB among women at risk of preeclampsia and found no effect.

Low molecular weight heparin and aspirin did not reduce risk of PTB when compared to aspirin alone among women with inherited thrombophilia (4 trials, 222 women, RR 0.99 (0.4–2.08) (Areia et al., 2016).

A Cochrane review (Khanprakob et al., 2012) identified one trial (98 women) randomized to a COX inhibitors (refecoxib) compared to placebo and identified an increased risk of PTB in the comparison group (RR 1.65, 95% CI 1.11–2.45).

4 *Antibiotics*: The use of antibiotics was evaluated in nine reviews.

Interventions that did not affect the preterm birth rate included: antibiotics for premature rupture of membranes (Kenyon et al., 2013; 3 trials, 4931 women), any treatment for bacterial vaginosis or trichomoniasis (Okun et al., 2005, 11 trials, 6052 women; Blocklehurst et al., 2013, 13 trials, 6491 women), nitrofurantoin prophylaxis for recurrent urinary tract infections (Schneeberger et al., 2015); 1 trial, 147 women), and prophylactic prenatal antibiotics (Thinkhamrop et al. 2015), 2 trials, 758 women).

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One review (Lamont et al., 2011; 5 trials, 2346 women) found that clindamycin for treatment of bacterial vaginosis reduced PTB risk (RR 0.60, 95% CI 0.42 to 0.86), while metronidazole for trichomoniasis was associated with an increased risk in one review (Gülmezoglu et al., 2011; 1 trial, 604 women, RR 1.78, 95% CI 1.19–2.66). Treatment of vaginal candidiasis was associated with a reduction in PTB risk in one review (Roberts et al., 2015; 2 trials, 685 women, RR 0.36, 95% CI 0.17-0.75).

5 *Progesterone*: Ten reviews evaluated progesterone supplementation in women with high risk pregnancies.
   a Women with singleton pregnancies and previous preterm bith: Progesterone (oral or intramuscular) was an effective PTB prevention strategy in women with singleton gestations and with previous preterm birth in two reviews. Likis et al. (2012) included 5 trials and 372 women and showed a RR 0.78 (95% CI 0.68 to 0.88) among women on any form of progesterone compared to an unspecified control. Dodd et al., (2013) included 10 trials, 1750 women, and found a RR 0.55 (95% CI 0.42 to 0.74) with progesterone supplementation compared to placebo or no treatment. One review (Saccone et al., 2016) reported that daily vaginal progesterone (either suppository or gel) is a better alternative to weekly intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) in preventing PTB < 34 weeks (3 trials, 680 women, RR 0.71, 95% CI 0.53-0.95, low quality evidence) and PTB < 32 weeks (RR 0.62, 95% CI 0.40-0.94, low quality evidence).
   b Multiple gestations: Progesterone supplementation for unselected women with multiple pregnancies did not reduce PTB in three reviews: Likis et al., 2012; 4 trials, unspecified number of women, RR 1.02, 95% CI 0.87–1.17; Dodd et al., 2013; 8 trials, 2674 women, RR 1.04, 95% CI 0.95-1.14. Schuit et al. (2015) was an IPD meta-analysis on twin pregnancies that defined gestational age at delivery to include intrauterine fetal demise. Neither vaginal progesterone (7 trials, 929 women, RR 0.97, 95% CI0.85-1.10) nor intramuscular progesterone (6 trials, 2021 women, RR 1.10, 95% CI 0.94–1.20) reduced PTB when compared to placebo or no treatment.
   c Women in preterm labour: Progesterone for women in preterm labour was found to be effective in one review (Likis et al., 2012; 5 trials, unspecified number of women, RR 0.62, 95% CI 0.47 to 0.79) but supplementation for women in threatened preterm labour (and not in active PTL) did not show a benefit in another review (Dodd et al., 2013; 2 trials, 223 women, RR 0.51, 95% CI 0.20–1.31).
   d Sonographically short cervix: Progesterone for women with sonographically short cervix did not reduce risk of PTB < 37 weeks in four reviews (Dodd et al., 2013; 3 trials, 1303 women, RR 0.97, 95% CI 0.82–1.15; Conde-Agudelo et al., 2013; 4 trials, 158 women, RR 0.84, 95% CI 0.61–1.14; Romero et al., 2016, 5 trials, 723 women, RR 0.89, 95% CI 0.74–1.08). However, the IPD meta-analysis by Romero et al. (2016) found a significant reduction in PTB ≤ 34 weeks or fetal death (5 trials, 974 women, RR 0.66, 95% CI 0.52-0.83), PTB < 34 weeks only (RR 0.60, 95% CI 0.44-0.82) and spontaneous PTB < 34 weeks (RR 0.63, 95% CI 0.44-0.88), and at earlier gestational ages (PTB < 32 weeks, RR 0.56, 95% CI 0.38-0.82; and PTB < 28 weeks, RR 0.51, 95% CI 0.31-0.85). One review also compared progesterone to cerclage in women with short cervix (Conde-Agudelo et al., 2013) and found no difference (unspecificed number of trials, RR 1.20, 95% CI 0.84–1.72).
   e Any risk factors for PTB: Progesterone in women with any risk factors for PTB was evaluated in three reviews (Coomarasamy et al., 2006; Dodd et al., 2013; Sotiriadis et al., 2012). Only one found a reduction in PTB risk (Coomarasamy et al., 2006; 8 trials, unspecified number of women) with a RR 0.42 (95% CI 0.31 to 0.57). One (Sotiriadis et al., 2012) did not identify any applicable trials.

6 *Other medications*: L-arginine was evaluated in one review. Dorniak-Wall et al. (2014) found a reduction in PTB risk (RR 0.48, 95% CI 0.28 to 0.81) in women at risk for preeclampsia treated with L-arginine versus placebo (1 trial, 672 women). Levothyroxine was found to reduce risk of PTB among women with thyroid disease when compared to no treatment (Reid et al., 2013; 1 trial, 115 women; RR 0.28, 95% CI 0.10 to 0.80). Oral betamimetics in twin pregnancies was not found to reduce PTB risk when compared to placebo or other interventions to prevent PTB (Yamasmit et al., 2015; 4 trials, 276 women, RR 0.85, 95% CI 0.65–1.1).

7 *Models of health care*: Two reviews evaluated specialized models of antenatal care among women at high risk for PTB. Dodd et al. (2015) set out to evaluate specialized antenatal care for women with twin gestations and did not indentify any eligible studies that assessed PTB risk, although they did report on neonatal outcomes including an increased risk of NICU admission (RR 1.43, 95% CI 1.02–2.00) and C-section rate (RR 1.38, 95% CI 1.06–1.81). Whitworth et al., (2011) included 3 trials and 3400 women and compared specialized care to standard care in women with singleton pregnancies at risk for PTB. There was no difference detected in risk for PTB (RR 0.87, 95% CI 0.69–1.08).

8 *Nutritional supplements*: Antioxidants for women at risk of preeclampsia (Rumbold et al., 2008; 3 trials, 3131 women, RR 1.09, 95% CI 0.97–1.22), long chain polyunsaturated fatty acids for women at risk of PTB (Horvath et al., 2007; 4 trials, 523 women, RR 0.82, 95% CI 0.60–1.12), omega-3 for women with previous PTB (Saccone et al., 2015a; 2 women, 1080 women, RR 0.81, 95% CI 0.59–1.21), calcium in women with low intake (Hofmeyr et al., 2015; 7 trials, 10242 women, RR 0.81, 95% CI 0.64–1.02), selenium (Reid et al., 2013; 1 trial, 169 women, RR 0.96, 95% CI 0.20–4.61), and vitamin A among HIV positive women (Wiysonge et al., 2011, 3 trials, 2110 women, RR 0.88, 95% CI 0.65–1.19) did not have effects on PTB in high-risk women. Calcium supplementation was found to reduce risk of PTB in women at risk of hypertensive disorders in one review (Hofmeyr et al., 2015, 4 trials, 568 women, RR 0.45, 95% CI 0.24 to 0.83).

9 *Psychosocial interventions*: One review found that smoking cessation or relapse prevention programs for high risk women resulted in a reduced risk of PTB when compared to usual care, less intensive care or alternative care, based on 14 reviews and 7852 women (Chamberlain et al., 2013), RR 0.82 (95% CI 0.71 to 0.96). There was no significant effect on PTB with social support for women at high risk of PTB (Hodnett et al., 2010; 17 trials, 12,264 women, RR 0.92, 95% CI 0.83–1.01), relaxation therapy for women in preterm labour (Khianman et al., 2012; 1 trial, 120 women, RR 0.95, 95% CI 0.57–1.59), or “any psychosocial intervention” for teenage pregnant women (Sukhato et al., 2015; 4 trials, 684 women, RR 0.67, 95% CI 0.42–1.05).

10 *Screening +/- treatment*: Berghella et al., (2011) showed that cervical length screening in singleton gestations with history of preterm birth, and placement of cerclage in women with short cervix resulted in a PTB reduction comparable to cerclage placement based on history only (4 trials, 467 women, RR 0.97, 95% CI 0.73–1.29).

11 *Cerclage and pessary*: Women at risk of preterm birth who had a cerclage had a lower risk of preterm birth than women

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without cerclage (Alfirevic et al., 2012; 9 trials, 2898 women, RR 0.80, 95% CI 0.69-0.95). Three reviews evaluated two specific subpopulations of women. An IPD meta-analysis by Berghella et al. (2010) evaluated the effectiveness of cerclage for women with singleton pregnancies and short cervix <25 mm on midtrimester ultrasound and found a decreased risk of PTB (4 trials, 552 women, RR 0.79, 95% CI 0.65-0.95). A non-Cochrane review by Berghella et al. (2011b) looked at cerclage for asymptomatic women with singleton gestation, history of preterm birth, and short midtrimester cervical length on ultrasound and found a decreased risk of PTB as well (5 trials, 874 women, RR 0.70, 95% CI 0.58-0.83). These results were supported by Conde-Agudelo et al. (2013), whose population also included singleton pregnancies with short midtrimester ultrasound and history of preterm birth and who found a RR 0.70, 95% CI 0.58-0.83, across 5 trials and 504 women.

Two reviews investigated cerclage for multiple pregnancies and both identified a nonsignificant effect on PTB (Rafael et al., 2014; 5 trials, 128 women, RR 1.12, 95% CI 0.89–1.43; and Liu et al. 2013; 5 trials, 310 women, RR 1.01, 95% CI 0.77–1.33).

One Cochrane review assessed cervical pessary versus expectant management in singleton gestations with short cervix of 25 mm or less, and found a reduction in PTB (Abdel-Aleem et al., 2013; 1 trial, 385 women; RR 0.36, 95% CI 0.27 to 0.49).

12 *Treatment of periodontal disease*: Two out of the nine reviews that evaluated this intervention showed a significant reduction in PTB in women with periodontal disease who receive treatment (George et al., 2011: 10 trial, 5496 women, RR 0.65, 95% CI 0.45 to 0.93; Uppal et al., 2010; 10 trials, 6142 women, RR 0.59, 95% CI 0.40 to 0.88).

But a majority of reviews found no effect on PTB for this intervention. Schwendicke et al. (2015) evaluated subgingival scaling and root planning with or without adjunct antibiotics for women with periodontal disease (5 trials, unspecified number of women, OR 0.79, 95% CI 0.57–1.10). Boutin et al. (2013) also evaluated periodontal treatment for women with periodontal disease but included a wide range of control groups including no care, hygiene education, or supragingival treatment (12 trials, 7018, RR 0.89, 95% CI 0.73–1.08). Chambrone et al. (2011) compared scaling and root planning with or without antibiotics for plaque induced ginigivitis to no treatment, supragingival debridement and tooth polishing (11 trials, 5752 women, RR 0.88, 95% CI 0.72–1.09). Fogacci et al. (2011) compared treatment of destructive periodontal disease or periodontitis to no treatment or dental plaque instruction, prophylaxis, or supragingival scaling. Risk of PTB was reported controlled for multiparity on the basis that it was the largest number of trials for this outcome (8 trials, 5270 women, RR 0.92, 95% CI 0.72–1.17). Kim et al. (2012) compared scaling and root planning to placebo or no treatment (11 trials, 5655 women, RR 0.81, 95% CI 0.64–1.01). An earlier comparison of scaling and root planning to placebo or no treatment conducted by Polyzos et al. (2010) identified 11 trials, 6558 women, and RR 0.93, 95% CI 0.79-1.10. Rosa et al. (2012) used more stringent inclusion criteria and compared periodontal treatment to standard care for women with singleton gestation at 22 weeks of less and stringent criteria for definiting periodontal disease. They identified 13 trials, 6988 women, and no effect on PTB (RR 0.90, 95%CI 0.68–1.19).

IV **Secondary outcomes–secondary prevention:**

Perinatal, fetal or neonatal mortality were generally not different with the following secondary prevention interventions: cervical cerclage in high risk women (Alfirevic et al., 2012; Berghella and MacKeen, 2011a and b; Conde-Agudelo et al., 2013, Jorgensen et al., 2007, Rafael et al., 2014, Saccone et al. 2015b; Meher et al., 2017), antiplatelet agents in women at risk for preeclampsia (Askie et al, 2007; Roberge et al., 2013; Xu et al., 2015; Cristina et al., 2009), treatment for vaginitis (Brocklehurst et al., 2013; Lamont et al., 2011; Okun et al., 2005), routine prophylactic antibiotics (Thinkhamrop et al., 2015), antibiotics for premature rupture of membranes (Kenyon et al., 2013), planned early delivery for women with premature rupture of membranes (Buchanan et al., 2010), psychosocial interventions for smoking cessation (Chamberlain et al., 2013), nicotine replacement for smoking cessation (Coleman et al., 2011), antenatal bedrest for multiple gestation (Crowther et al., 2010), specialized antenatal care in women with multiple gestation (Dodd et al., 2015) and in women at risk of having a preterm or growth restricted baby (Hodnett et al., 2010; Whitworth et al., 2011), periodontal treatment for women with periodontal disease (George et al., 2011; Polyzos et al., 2010; Schwendicke et al., 2015), calcium supplementation (Hofmeyr et al., 2014), long chain polyunsaturated fatty acid supplementation (Horvath et al., 2007) and omega 3 (Saccone & Berghella, 2015a), vitamin A for HIV positive women (Wiysonge et al., 2011), and home uterine monitoring (Urquhart et al., 2015),

Progesterone in high risk women did not have a significant effect on perinatal mortality in multiple reviews (Conde-Agudelo et al., 2013; Dodd et al., 2013; Likis et al., 2012; Romero et al., 2012, and 2016; Schuit et al., 2015; Sotiriadis et al., 2012; Combs et al., 2012), except in women with a singleton pregnancy and history of PTB. In this subpopulation, Dodd et al., (2013) showed decreased perinatal mortality (RR 0.50, 95% CI 0.33 to 0.75), neonatal mortality (RR 0.45, 95% CI 0.27 to 0.76), low birth weight (RR 0.58, 95% CI 0.42 to 0.79), and NICU admission (RR 0.24, 95% CI 0.14 to 0.40). Likis et al. (2012) also showed decreased neonatal mortality with progesterone in a subpopulation of women with previous preterm birth (RR 0.58, 95% CI 0.27 to 0.98), asymptomatic short cervix (RR 0.40, 95% CI 0.09 to 0.91), and women with preterm labour, but not in multiple gestations. Risk of low birth weight was also decreased in women with previous PTB (RR 0.66, 95%CI 0.51 to 0.87). There was a reduced risk of NICU admission with progesterone in women with short cervix and singleton pregnancies (Romero et al., 2016), women with singleton gestation, short cervix and history of preterm birth (Conde-Agudelo et al., 2013), and a reduced risk with vaginal progesterone compared to intramuscular progesterone in asymptomatic singletons with history of PTB (Saccone et al., 2016).

Sealing procedures for women with premature rupture of membranes was shown to reduce neonatal mortality (RR 0.38, 95% CI 0.19 to 0.75) in one review (Crowley et al., 2016).

The other secondary outcomes were assessed in few reviews and most interventions had no effect. Psychosocial programs (Chamberlain et al., 2013) and nicotine replacement therapy (Coleman et al., 2011) for smoking cessation were found to reduce risk of low birth weight. Periodontal treatment was also found to reduce LBW in one review (George et al. 2011).

Data for maternal outcomes were rarely available. There was no difference in maternal satisfaction with vaginal progesterone compared to control (Dodd et al., 2013) and in women with multiple gestation receiving specialized antenatal care (Dodd et al., 2015).

Discussion

Key findings

This review of reviews aimed to systematically assess existing literature regarding effectiveness and safety of interventions to prevent PTB.In total, 112 reviews were included.

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Sixty reviews assessed the effect of primary prevention interventions on risk of PTB. Positive effects were found for lifestyle and behavioural changes, including diet and exercise; nutritional supplements, including calcium and zinc supplementation; nutritional education; screening for lower genital tract infections. However, there were no or minimal data available for most of our secondary outcomes.

There were 83 systematic reviews of secondary prevention interventions. Positive effects were found for low dose aspirin among women at risk of preeclampsia; clindamycin for treatment of bacterial vaginosis and treatment of vaginal candidiasis; progesterone in women with prior spontaneous PTB and in those with short midtrimester cervical length; L-arginine in women at risk for preeclampsia; levothyroxine among women with thyroid disease; calcium supplementation in women at risk of hypertensive disorders; smoking cessation; cervical length screening in high-risk singleton gestations; cervical pessary in singleton gestations with short cervix; and treatment of periodontal disease. COX inhibitors and metronidazole for trichomoniasis seem to be associated with an increased risk of PTB.

Our results may be influenced by the methodological quality of the included reviews and RCTs. Interventions that may have an effect on PTB but are used for other conditions could potentially have been missed, however we used a broad search strategy to minimize this risk. The major shortcoming of a review of reviews is the loss of more detailed information by qualitatively aggregating information. For example, women at risk of PTB were defined precisely in some reviews, but not in others.

The prevention of prematurity is a rapidly evolving maternal and child health topic. Therefore, summarizing evidence of this topic is an important priority.

This article is, to our knowledge, the first review of reviews on primary and secondary prevention of PTB that has considered all forms of systematic reviews as well as a review of planned and ongoing trials. The possible effects of a diverse range of interventions for primary and secondary prevention of PTB have been evaluated in several systematic reviews of RCTs. Altough there is a large number of reviews, few interventions have been definitvely demonstrated to be safe and effective. For several of the interventions evaluated, there was insufficient evidence to assess whether the intervention was effective or not. There is little high-quality evidence for most of the interventions studied, which should be taken into account when making magenement decisions.

The difficulty in interpreting the results of this review highlights the importance of having a specific population to be studied in trials on PTB, such as those at risk of PTB, and conducting RCTs in comparing interventions. There should be an agreed-upon set of clearly-defined and measurable outcomes, including maternal secondary outcomes such as maternal deths, satisfaction, admission to intensive care unit, in future PTB intervention trials, so that outcomes of trials can be easily meta-analysed The vast majority of the trials in included reviews were small; review authors often emphasized the need for larger, well-designed RCTs.

Disclosure

The authors report no conflict of interest.

Financial support

At the time of conducting this review of systematic reviews, JPV was employed at the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research. JPV is currently employed by the Burnet Institute (Melbourne, Australia).

Condensation

Only a few interventions have been demononstrated to be effective in primary and secondary prevention of preterm birth, including cerclage, progesterone, low dose aspirin, and lifestyle and behavioural changes.

Authors contribution

All authors contributed equally to this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2018.12.022.

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