
Effects of micronutrient supplementation during pregnancy on birth, child health and development outcomes: a systematic review

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Title of the review

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Background

Micronutrient deficiencies are widespread among women of reproductive age (WRA) in low- and middle-income countries (LMICs) (Black, 2013), largely as a result of diets that lack diversity and thus do not provide sufficient amounts of essential vitamins and minerals (FAO & WHO, 2004). Because of increased nutritional requirements throughout pregnancy, deficiencies are often exacerbated during this time and have been associated with several adverse outcomes for both the mother and the baby (Berti, 2011; Black, 2001; Dunn, 1993; Haider, 2013; De-Regil, 2015).

To overcome the complications associated with micronutrient deficiencies during pregnancy, supplementation has been recommended as part of routine antenatal care. The World Health Organization (WHO) currently recommends iron folic acid supplementation or, in places where anaemia is a severe public health problem, iron supplementation alone (WHO, 2012). To address the issue of multiple deficiencies, the United Nations Children's Fund (UNICEF), United Nations University (UNU), and the WHO developed a multiple-micronutrient tablet that provides the daily recommended intake of vitamin A, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, and iodine with 30mg iron and 15mg of zinc for pregnant women (UNICEF, WHO & UNU, 1999).

Results from micronutrient supplementation efficacy trials have demonstrated notable improvements for various outcomes (Haider, 2017; Hodgetts, 2015; Lassi, 2013; Pena-Rosas, 2015) and, as such, supplementation strategies have been absorbed into nutritional and antenatal care programmes in many LMICs. However, compliance can be an issue, indicating that in a real life setting pregnant women may not be gaining all the potential benefits of supplementation.

This review aims to synthesize the existing evidence on prenatal micronutrient supplementation, both from trials and existing programmes in LMICs. We will investigate a broad range of maternal and child health outcomes, including potential adverse effects, which are relevant to policy and programming in these settings. This approach will enable a comprehensive assessment of the effectiveness of micronutrient supplementation during pregnancy for improving maternal and child health, birth, and development outcomes.

Objectives

1. What is the effectiveness of iron folic acid supplementation during pregnancy on birth, child health and development outcomes?
2. What is the effectiveness of multiple micronutrient supplementation during pregnancy on birth, child health and development outcomes?
3. What is the effectiveness of single micronutrient supplementation (calcium, vitamin D, iodine) during pregnancy on birth, child health and development outcomes?
4. What is the effectiveness of lipid-based nutrient supplementation during pregnancy on birth, child health and development outcomes?

Existing reviews

Objective 1: Iron folic acid supplementation

Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015 Oct 19;(10):CD009997. doi:10.1002/14651858.CD009997.pub2.

Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015, Issue 7. Art. No.: CD004736. doi:10.1002/14651858.CD004736.pub5.

Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW; Nutrition Impact Model Study Group (anaemia). Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2013;21;346:f3443. doi:10.1136/bmj.f3443.

Objective 2: Multiple micronutrient supplementation

Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2017 Apr 13;4:CD004905. doi:10.1002/14651858.CD004905.pub5.

Suchdev PS, Peña-Rosas JP, De-Regil LM. Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women. *Cochrane Database Syst Rev* 2015, Issue 6. Art. No: CD011158. doi:10.1002/14651858.CD011158.pub2.

Objective 3: Single micronutrient supplementation

Lassi ZS, Salam RA, Haider BA, Bhutta ZA. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. *Cochrane Database Syst Rev* 2013 Mar 28;(3):CD006896. doi:10.1002/14651858.CD006896.pub2.

Hodgetts VA, Morris RK, Francis A, Gardosi J, Ismail KM. Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. *BJOG* 2015;122:478–90.

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database Syst Rev* 2015, Issue 2. Art. No.: CD007079. doi:10.1002/14651858.CD007079.pub3.

Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014, Issue 6. Art. No.: CD001059. doi:10.1002/14651858.CD001059.pub4.

Harding KB, Peña-Rosas JP, Webster AC, Yap CMY, Payne BA, Ota E, De-Regil LM. Iodine supplementation for women during the preconception, pregnancy and postpartum period. *Cochrane Database Syst Rev* 2017, Issue 3. Art. No.: CD011761. doi:10.1002/14651858.CD011761.pub2

De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2016, Issue 1. Art. No: CD008873. doi:10.1002/14651858.CD008873.pub3.

Objective 4: Lipid-based nutrient supplementation

Das JK, Salam RA, Weise PZ, et al. Lipid-based nutrient supplements for pregnant women and their impact on pregnancy, birth, and infant developmental outcomes in stable and emergency settings. 2017 *Cochrane (review protocol)*.

Intervention

The following interventions targeting pregnant women will be included:

- Single micronutrient supplementation (calcium, vitamin D, iodine, folic acid, vitamin A, zinc) compared to placebo or supplements without the micronutrient of interest
 - Supplementation may take the form of tablets, drops, syrup, or powder
- Iron folic acid supplementation compared to folic acid alone or placebo or supplements without iron or folic acid
- Vitamin D and calcium supplementation compared to placebo or supplements without vitamin D or calcium
- Multiple micronutrient supplementation compared to iron folic acid supplementation
 - Trials that use fewer than 3 micronutrients in the composition of the MMN supplement will be excluded
- Lipid-based nutrient supplementation compared to multiple micronutrient supplementation or placebo

Population

The target population is healthy (i.e. non-diseased) pregnant women of any age or parity living in low- and middle-income countries (as defined by the World Bank). As such, our review will include all women of reproductive age, including adolescent girls (10-19 years). Outcomes will pertain to both mothers and their infants, where applicable.

Outcomes

For simplification, we have split all secondary outcomes of interest by maternal, fetal, newborn, child, and other outcomes.

Primary outcomes

- Anemia/iron-deficiency anemia in pregnancy
- Low birth weight (<2500 g)
- Perinatal mortality (stillbirths and deaths ≤ 7 days)

Secondary outcomes

Maternal Outcomes

Mortality:

- Maternal death (death while pregnant or within 42 days of pregnancy termination)

Morbidity:

- Pre-eclampsia/eclampsia
- Gestational hypertension
- Antepartum haemorrhage
- Postpartum haemorrhage
- Premature rupture of membranes
- Placental abruption
- Infections during pregnancy
- Clinical malaria
- Bone mineral density
- Incidence of fracture
- Hypothyroidism
- Thyroid size
- Night blindness
- Need for blood transfusion

Biochemical status:

- Micronutrient deficiencies
 - Vitamin A (serum/plasma retinol)
 - Iron (serum/plasma ferritin, plasma TfR, TIBC)
 - Serum/plasma/red blood cell folate
 - Serum/plasma zinc
 - Serum/plasma vitamin D (25-hydroxyvitamin D)
- Thyroglobulin concentration

Fetal Outcomes

Mortality:

- Miscarriage (loss of pregnancy before 28 weeks gestation)
- Stillbirth (death at or beyond 28 weeks' gestation)

Morbidity:

- Congenital anomalies

Newborn Outcomes

Mortality:

- Neonatal mortality (deaths between 0 and 28 days)

Morbidity:

- Preterm birth (<37 weeks gestation)
- Small-for-gestational age (defined by study authors)
- Macrosomia (birthweight >4000 g)

Anthropometry:

- Birthweight (g)
- Birth length (cm)
- Head circumference (cm)

Child Outcomes

Mortality:

- Infant mortality (deaths between 0 and 12 months)
- Under-five mortality (deaths between 0 and 59 months)

Morbidity:

- Stunting (-2 z-score or lower)
- Wasting (-2 z-score or lower)
- Underweight (-2 z-score or lower)
- Bone mineral density
- Fracture
- Rickets
- Hypothyroidism or elevated thyroid stimulating hormone (TSH)
- Development outcomes (as defined by study authors)
- Infection
- Respiratory disease
- Allergic disease

Biochemical status:

- Micronutrient deficiencies
 - Vitamin A (serum/plasma retinol)
 - Iron (serum/plasma ferritin, plasma TfR)
 - Serum/plasma/red blood cell folate
 - Serum/plasma zinc
 - Serum/plasma vitamin D (25-hydroxyvitamin D)
- Anaemia
 - Hemoglobin concentration
- Iron deficiency anaemia

Other Outcomes

- Relevant long-term outcomes during adolescence or adulthood, as specified by trial authors. For example:
 - Anthropometrics (stunting, wasting, underweight)
 - Cognitive and motor development, as assessed by trialists (e.g. Bayley Mental Development Index, Bayley Psychomotor Development Index, Stanford-Binet test)
 - Educational attainment (completion of primary or secondary school)
- Mode of delivery (vaginal, instrumental vaginal, caesarean)
- Adverse outcomes: any reported throughout intervention period (e.g. urinary tract infections, kidney stones, hyperthyroidism, allergic reactions, etc.), including short-term adverse outcomes (e.g. vomiting, abdominal pain, constipation, diarrhea, unpleasant tastes)

Study designs

We will include primary studies, including large-scale programme evaluations, which assess the efficacy and/or effectiveness of interventions using experimental and quasi-experimental study designs that allow for causal inference:

1. Studies where participants were randomly assigned, individually or in clusters, to intervention and comparison groups.
2. Studies where non-random assignment to intervention and comparison groups is based on other known allocation rules, including a threshold on a continuous variable (regression discontinuity designs) or exogenous geographical variation in the treatment allocation (natural experiments).
3. Controlled before-after studies in which allocation to intervention and control groups was not made by study investigators, and outcomes were measured in both intervention and control groups at baseline, and appropriate methods were used to control for selection bias and confounding, such as statistical matching (e.g., propensity score matching, or covariate matching) or regression adjustment (e.g., difference-in-differences, instrumental variables).
4. Interrupted time series studies in which outcomes were measured in the intervention group at least three time points before the intervention was implemented and at least three time points after.

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Roles and responsibilities

Emily Keats and Aamer Imdad have methodological, statistical, and information retrieval expertise. Zulfiqar Bhutta has content expertise. All additional team members (to be determined) will receive training in systematic review methods.

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Potential conflicts of interest

The authors are not aware of any conflicts of interest arising from financial or researcher interests.

Preliminary timeframe

- Date we plan to submit a draft protocol: 30 January 2018
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