

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoffman 2009

Hoffman C, Galan HL. Assessing the 'at-risk' fetus: doppler ultrasound. *Current Opinion in Obstetrics and Gynecology* 2009;**21**(2):161–6.

Hofmeyr 2011

Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2010, Issue 8. [DOI: 10.1002/14651858.CD001059.pub3]

Hussain 2011

Hussain AA, Yakoob MY, Imdad A, Bhutta ZA. Elective induction for pregnancies at or beyond 41 weeks of gestation and its impact on stillbirths: a systematic review with meta-analysis. *BMC Public Health* 2011;**11 Suppl 3**:S5.

Imdad 2011

Imdad A, Yakoob MY, Bhutta ZA. The effect of folic acid, protein energy and multiple micronutrient supplements in pregnancy on stillbirths. *BMC Public Health* 2011;**11 Suppl 3**:S4.

Jabeen 2011

Jabeen M, Yakoob MY, Imdad A, Bhutta ZA. Impact of interventions to prevent and manage preeclampsia and eclampsia on stillbirths. *BMC Public Health* 2011;**11 Suppl 3**:S6.

Kirksey 1994

Kirksey A, Wachs TD, Yunis F, Srinath U, Rahmanifar A, McCabe GP, et al. Relation of maternal zinc nutrition to pregnancy outcome and infant development in an Egyptian village. *American Journal of Clinical Nutrition* 1994;**60**:782–92.

Lawn 2011

Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count?. *Lancet* 2011;**377**(9775):1448–63.

Mathews 1999

Mathews F, Yudkin P, Neil A. Influence of maternal nutrition on outcome of pregnancy: prospective cohort study. *BMJ* 1999;**319**:339–43.

McClure 2006

McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. *International Journal of Gynecology & Obstetrics* 2006;**94**(2):82–90.

McClure 2007

McClure EM, Goldenberg RL, Bann CM. Maternal mortality, stillbirth and measures of obstetric care in developing and developed countries. *International Journal of Gynecology & Obstetrics* 2007;**96**(2):139–46.

McClure 2009

McClure EM, Saleem S, Pasha O, Goldenberg RL. Stillbirth in developing countries: a review of causes, risk factors and prevention strategies. *Journal of Maternal-Fetal and Neonatal Medicine* 2009;**22**(3):183–90.

Menzies 2007

Menzies J, Magee LA, Li J, MacNab YC, Yin R, Stuart H, et al. Instituting surveillance guidelines and adverse outcomes in preeclampsia. *Obstetrics & Gynecology* 2007;**110**(1):121–7.

Moher 2007

Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. *PLoS Medicine* 2007;**4**(3):e78.

Norwitz 2007

Norwitz ER, Snegovskikh VV, Caughey AB. Prolonged pregnancy: when should we intervene?. *Clinical Obstetrics and Gynecology* 2007;**50**(2):547–57.

Pattinson 2011

Pattinson R, Kerber K, Buchmann E, Friberg IK, Belizan M, Lansky S et al for The Lancet's Stillbirths Series steering committee. Stillbirths: how can health systems deliver for mothers and babies?. *Lancet* 2011;**377**(9777):1610–23.

Rumbold 2006

Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS, for the ACTSSG. Vitamins C and E and the risks of preeclampsia and perinatal complications. *New England Journal of Medicine* 2006;**354**:1796–806.

Salihu 2007

Salihu HM, Wilson RE. Epidemiology of prenatal smoking and perinatal outcomes. *Early Human Development* 2007;**83**(11):713–20.

Sanchez-Ramos 2003

Sanchez-Ramos L, Olivier F, Delke I, Kaunitz AM. Labor induction versus expectant management for postterm pregnancies: a systematic review with meta-analysis. *Obstetrics & Gynecology* 2003;**101**(6):1312–8.

Schmid 2007

Schmid GP, Stoner BP, Hawkes S, Broutet N. The need and plan for global elimination of congenital syphilis. *Sexually Transmitted Diseases* 2007;**34**(7 Suppl):S5–S10.

Shea 2007

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10.

Shrimpton 2009

Shrimpton R, Huffman SL, Zehner ER, Darnton-Hill I, Dalmiya N. Multiple micronutrient supplementation during pregnancy in developing-country settings: policy and program implications of the results of a meta-analysis. *Food and Nutrition Bulletin* 2009;**30**:S556–S573.

Silver 2007

Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, et al. Work-up of stillbirth: a review of the

evidence. *American Journal of Obstetrics and Gynecology* 2007;**196**(5):433–44.

Smith 2007

Smith GC, Fretts RC. Stillbirth. *Lancet* 2007;**370**(9600): 1715–25.

U.S. 2004

U.S. Department of Health and Human Services. *The health consequences of smoking. 2004 Surgeon General's Report*. U.S. Department of Health and Human Services, 2004.

UN 2010

United Nations. Millennium Development Goals. UN Summit on the Millennium Development Goals (<http://www.un.org/millenniumgoals>) (accessed 2011).

Van Geertruyden 2004

Van Geertruyden JP, Thomas F, Erhart A, D'Alessandro U. The contribution of malaria in pregnancy to perinatal mortality. *American Journal of Tropical Medicine and Hygiene* 2004;**71**(2 Suppl):35–40.

Weiner 2003

Weiner R, Ronsmans C, Dorman E, Jilo H, Muhoro A, Shulman C. Labour complications remain the most important risk factor for perinatal mortality in rural Kenya. *Bulletin of the World Health Organization* 2003;**81**(8): 561–6.

WHO 1993

WHO. *International statistical classification of diseases and related health problems. Tenth revision*. Vol. 2, Geneva: World Health Organization, 1993.

WHO 1995

WHO. Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study: introduction. *Bulletin of the World Health Organization* 1995;**73** Suppl:1–6.

Yakoob 2010

Yakoob MY, Lawn JE, Darmstadt GL, Bhutta ZA. Stillbirths: epidemiology, evidence, and priorities for action. *Seminars in Perinatology* 2010;**34**(6):387–94.

* Indicates the major publication for the study

HISTORY

Protocol first published: Issue 1, 2012

CONTRIBUTIONS OF AUTHORS

Erika Ota (EO), João Paulo Souza (JPS) and Rintaro Mori (RM) participated in the study design. EO drafted the protocol. JPS, Ruoyan Tobe-Gai, RM, Philippa Middleton and Vicki Flenady provided critical comments and valuable suggestions.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

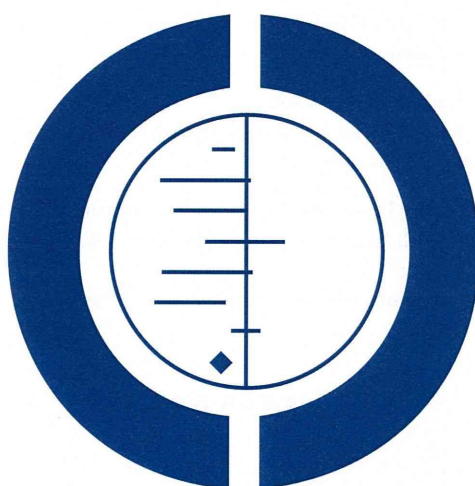
- The University of Tokyo, Department of Global Health Policy, Graduate School of Medicine, Japan.
- Department of Reproductive Health and Research and Department of Technical Cooperation among Countries, World Health Organization, Geneva, Switzerland.

External sources

- Ministry of Health, Labour and Welfare, Japan.

Antenatal dietary advice and supplementation to increase energy and protein intake (Review)

Ota E, Tobe-Gai R, Mori R, Farrar D



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 9

<http://www.thecochranelibrary.com>



Antenatal dietary advice and supplementation to increase energy and protein intake (Review)
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Antenatal dietary advice and supplementation to increase energy and protein intake

Erika Ota¹, Ruoyan Tobe-Gai², Rintaro Mori³, Diane Farrar⁴

¹Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. ²School of Public Health, Shandong University, Jinan, China. ³Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan. ⁴Maternal and Child Health, Bradford Institute for Health Research, Bradford, UK

Contact address: Erika Ota, Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo, 113-0011, Japan. e-i@umin.ac.jp.

Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2012.

Review content assessed as up-to-date: 22 December 2011.

Citation: Ota E, Tobe-Gai R, Mori R, Farrar D. Antenatal dietary advice and supplementation to increase energy and protein intake. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD000032. DOI: 10.1002/14651858.CD000032.pub2.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Gestational weight gain is positively associated with fetal growth, and observational studies of food supplementation in pregnancy have reported increases in gestational weight gain and fetal growth.

Objectives

To assess the effects of advice during pregnancy to increase energy and protein intake, or of actual energy and protein supplementation, on energy and protein intakes, and the effect on maternal and infant health outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (22 July 2011) and contacted researchers in the field. We updated the search on 12 July 2012 and added the results to the awaiting classification section of the review.

Selection criteria

Randomised controlled trials of dietary advice to increase energy and protein intake, or of actual energy and protein supplementation, during pregnancy.

Data collection and analysis

Two review authors independently assessed trials for inclusion and assessed risk of bias. Two review authors independently extracted data and checked for accuracy. Extracted data were supplemented by additional information from the trialists we contacted.

Main results

We examined 110 reports corresponding to 46 trials. Of these trials, 15 were included, 30 were excluded, and one is ongoing. Overall, 15 trials involving 7410 women were included.

Nutritional advice (four trials, 790 women)

Women given nutritional advice had a lower relative risk of having a preterm birth (two trials, 449 women) (risk ratio (RR) 0.46, 95% CI 0.21 to 0.98), head circumference at birth was increased in one trial (389 women) (mean difference (MD) 0.99 cm, 95% CI 0.43 to

Antenatal dietary advice and supplementation to increase energy and protein intake (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1.55) and protein intake increased (three trials, 632 women) (protein intake: MD +6.99 g/day, 95% CI 3.02 to 10.97). No significant differences were observed on any other outcomes.

Balanced energy and protein supplementation (11 trials, 5385 women)

Risk of stillbirth was significantly reduced for women given balanced energy and protein supplementation (RR 0.62, 95% CI 0.40 to 0.98, five trials, 3408 women), mean birthweight was significantly increased (random-effects MD +40.96 g, 95% CI 4.66 to 77.26, $\text{Tau}^2 = 1744$, $I^2 = 44\%$, 11 trials, 5385 women). There was also a significant reduction in the risk of small-for-gestational age (RR 0.79, 95% CI 0.69 to 0.90, $I^2 = 16\%$, seven trials, 4408 women). No significant effect was detected for preterm birth or neonatal death.

High-protein supplementation (one trial, 1051 women)

High-protein supplementation (one trial, 505 women), was associated with a significantly increased risk of small-for-gestational age babies (RR 1.58, 95% CI 1.03 to 2.41).

Isocaloric protein supplementation (two trials, 184 women)

Isocaloric protein supplementation (two trials, 184 women) had no significant effect on birthweight and weekly gestational weight gain.

Authors' conclusions

This review provides encouraging evidence that antenatal nutritional advice with the aim of increasing energy and protein intake in the general obstetric population appears to be effective in reducing the risk of preterm birth, increasing head circumference at birth and increasing protein intake, there was no evidence of benefit or adverse effect for any other outcome reported.

Balanced energy and protein supplementation seems to improve fetal growth, and may reduce the risk of stillbirth and infants born small-for-gestational age. High-protein supplementation does not seem to be beneficial and may be harmful to the fetus. Balanced-protein supplementation alone had no significant effects on perinatal outcomes.

The results of this review should be interpreted with caution, the risk of bias was either unclear or high for at least one category examined in several of the included trials and the quality of the evidence was low for several important outcomes. Also the anthropometric characteristics of the general obstetric population is changing, therefore, those developing interventions aimed at altering energy and protein intake should ensure that only those women likely to benefit are included. Large, well designed randomised trials are needed to assess the effects of increasing energy and protein intake during pregnancy in women whose intake is below recommended levels.

PLAIN LANGUAGE SUMMARY

Energy and protein intake in pregnancy

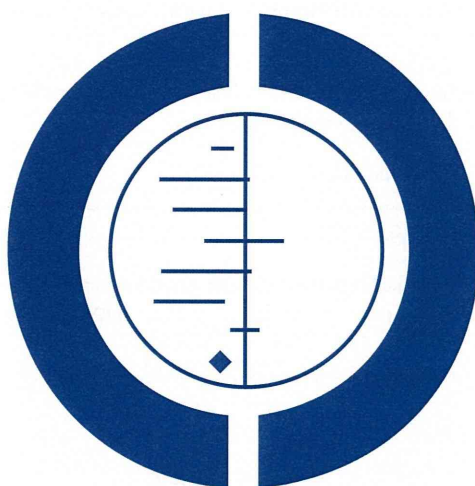
During pregnancy, a baby developing inside the womb receives all its nutrition from its mother. Therefore, advising women on their diet and providing food supplements in pregnancy may help babies to grow and thrive. This review of randomised controlled trials examined several aspects of dietary advice and supplementation and produced the following four findings.

- (1) Providing nutritional advice resulted in an increase in the mother's protein intake, fewer preterm births in two trials involving 449 women and increases in birth head circumference in one trial involving 389 women.
- (2) Giving the mothers balanced energy and/protein supplements was associated with clear increases in mean birthweight (11 trials, 5385 women) with fewer stillbirths (five trials, 3408 women) and fewer small-for-gestational age births (seven trials, 4408 women), but the impact on the long-term health of the baby was uncertain, including among undernourished women.
- (3) High-protein supplementation: one trial involving 1051 women showed no benefit for women and potential harm for the baby.
- (4) Isocaloric protein supplementations (i.e. balanced supplements in which the protein replaces an equal quantity of other nutrients, e.g. macronutrients, fat and carbohydrate): in two trials involving 184 women this intervention showed no benefit for women or their babies.

Providing nutritional advice or balanced energy and protein supplements to women during pregnancy may be beneficial; high-protein supplements and Isocaloric protein supplements given in to women in pregnancy may be unhelpful or harmful.

Zinc supplementation for improving pregnancy and infant outcome (Review)

Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 7

<http://www.thecochranelibrary.com>



Zinc supplementation for improving pregnancy and infant outcome (Review)
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Zinc supplementation for improving pregnancy and infant outcome

Rintaro Mori¹, Erika Ota², Philippa Middleton³, Ruoyan Tobe-Gai⁴, Kassam Mahomed⁵, Zulfiqar A Bhutta⁶

¹Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan. ²Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. ³ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. ⁴School of Public Health, Shandong University, Jinan, China. ⁵Ipswich Hospital, Ipswich, Australia. ⁶Division of Women and Child Health, Aga Khan University Hospital, Karachi, Pakistan

Contact address: Rintaro Mori, Department of Health Policy, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo, Tokyo, 166-0014, Japan. rintaromori@gmail.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2012.

Review content assessed as up-to-date: 1 March 2012.

Citation: Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD000230. DOI: 10.1002/14651858.CD000230.pub4.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

It has been suggested that low serum zinc levels may be associated with suboptimal outcomes of pregnancy such as prolonged labour, atonic postpartum haemorrhage, pregnancy-induced hypertension, preterm labour and post-term pregnancies, although many of these associations have not yet been established.

Objectives

To assess the effects of zinc supplementation in pregnancy on maternal, fetal, neonatal and infant outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2011) and reference lists of retrieved studies.

Selection criteria

Randomised trials of zinc supplementation in pregnancy. We excluded quasi-randomised controlled trials.

Data collection and analysis

Three review authors applied the study selection criteria, assessed trial quality and extracted data. When necessary, we contacted study authors for additional information.

Main results

We included 20 randomised controlled trials (RCTs) reported in 51 papers involving over 15,000 women and their babies. Trials were generally at low risk of bias. Zinc supplementation resulted in a small but significant reduction in preterm birth (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.97 in 16 RCTs; 16 trials of 7637 women). This was not accompanied by a similar reduction in numbers of babies with low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 trials of 5643 women). No significant differences were

Zinc supplementation for improving pregnancy and infant outcome (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

seen between the zinc and no zinc groups for any of the other primary maternal or neonatal outcomes, except for induction of labour in a single trial. No differing patterns were evident in the subgroups of women with low versus normal zinc and nutrition levels or in women who complied with their treatment versus those who did not.

Authors' conclusions

The evidence for a 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials involving women of low income and this has some relevance in areas of high perinatal mortality. There was no convincing evidence that zinc supplementation during pregnancy results in other useful and important benefits. Since the preterm association could well reflect poor nutrition, studies to address ways of improving the overall nutritional status of populations in impoverished areas, rather than focusing on micronutrient and or zinc supplementation in isolation, should be an urgent priority.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for improving pregnancy and infant outcome

Taking zinc during pregnancy helps to slightly reduce preterm births, but does not prevent other problems such as low birthweight babies.

Many women of childbearing age may have mild to moderate zinc deficiency. Low zinc concentrations may cause preterm birth or they may even prolong labour. It is also possible that zinc deficiency may affect infant growth as well. This review of 20 randomised controlled trials, involving over 15,000 women and their babies, found that although zinc supplementation has a small effect on reducing preterm births, it does not help to prevent low birthweight babies compared with not giving zinc supplements before 27 weeks' of pregnancy. No clear differences were seen for development of pregnancy hypertension or pre-eclampsia. The 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials of women with low incomes. In some trials all women were also given iron, folate or vitamins or combinations of these. UNICEF is already promoting antenatal use of multiple-micronutrient supplementation, including zinc, to all pregnant women in developing countries. Finding ways to improve women's overall nutritional status, particularly in low-income areas, will do more to improve the health of mothers and babies than supplementing pregnant women with zinc alone. In low-to-middle income countries, addressing anaemia and infections, such as malaria and hookworm, is also necessary.

