NUTRITIONAL INTERVENTIONS DURING PREGNANCY FOR THE PREVENTION OR TREATMENT OF MATERNAL MORBIDITY, MORTALITY OR PRETERM DELIVERY

OVERVIEW OF RANDOMISED CONTROLLED TRIALS

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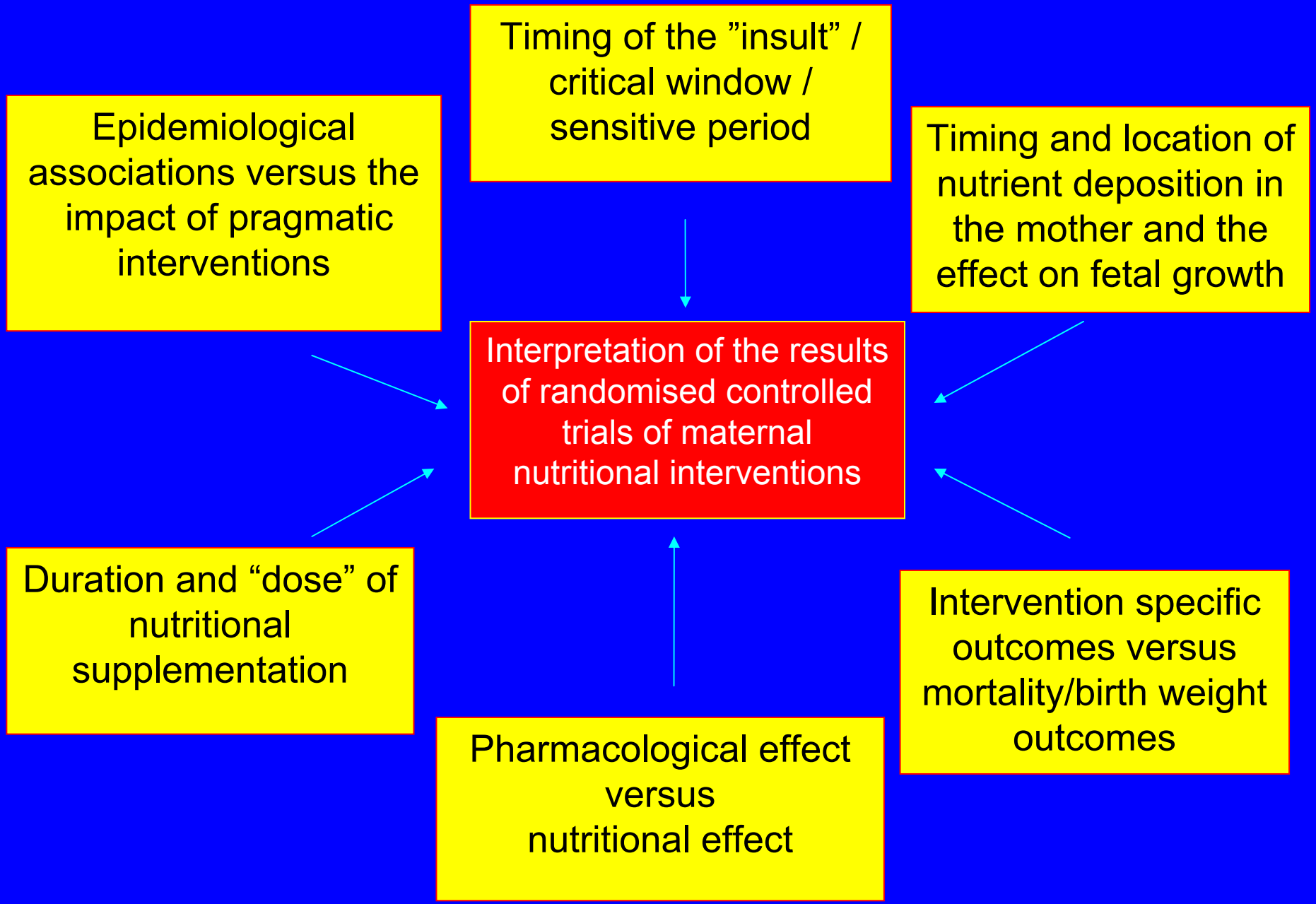
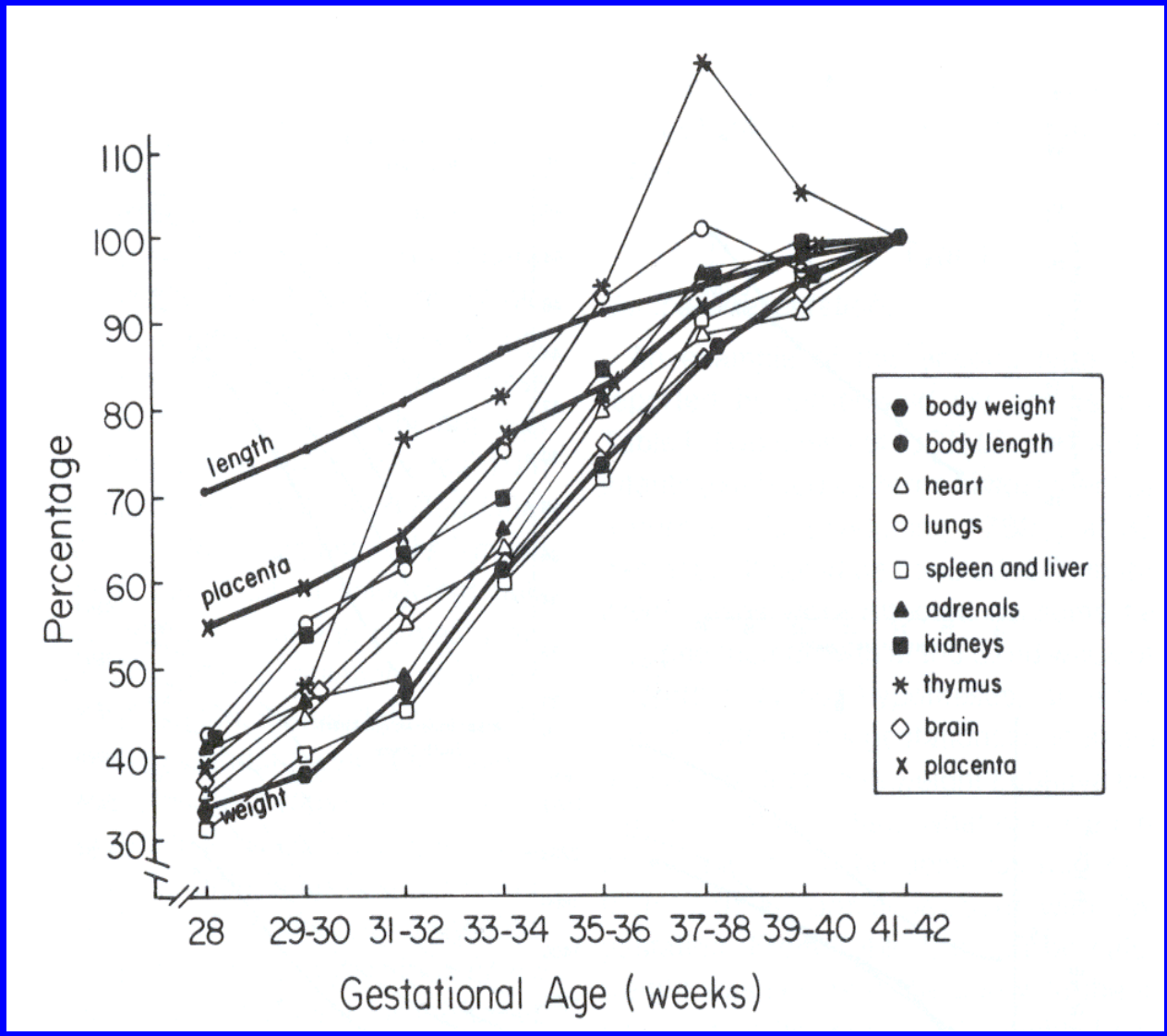
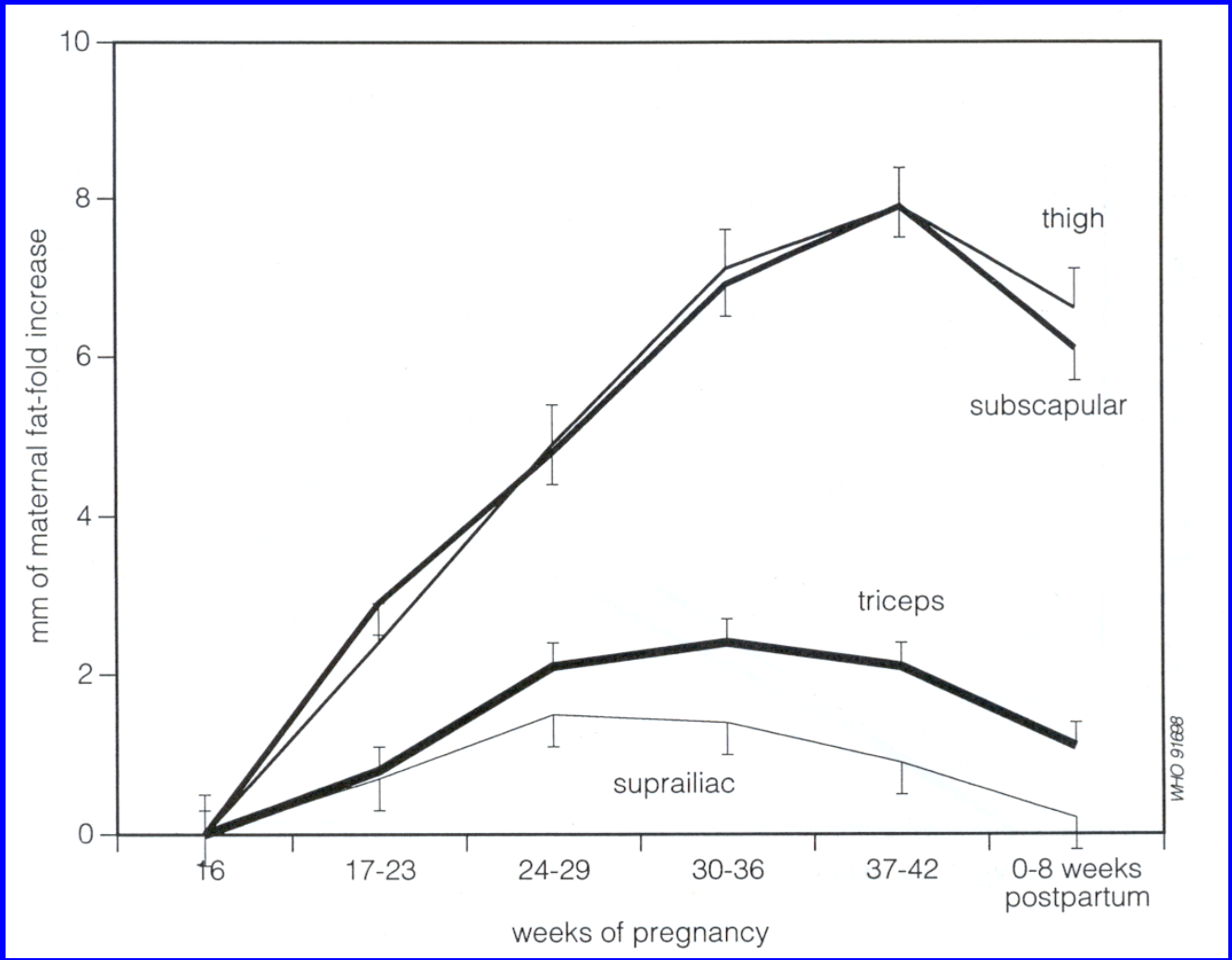

Timing of the ”insult” / critical window / sensitive period
Epidemiological associations versus the impact of pragmatic interventions
Timing and location of nutrient deposition in the mother and the effect on fetal growth
Interpretation of the results of randomised controlled trials of maternal nutritional interventions
Duration and “dose” of nutritional supplementation
Intervention specific outcomes versus mortality/birth weight outcomes
Pharmacological effect versus nutritional effect



Percentage of placental and organ weight of the total weight at term by week of gestation



Absolute changes in skin-fold thickness during pregnancy and post partum

SELECTION CRITERIA

- Any systematic review or randomised controlled trial of a nutritional intervention during pregnancy

SYSTEMATIC REVIEWS OR TRIALS REPORTING ONE OF THE FOLLOWING OUTCOMES:

- Preterm delivery (<37 completed weeks)
- Pre-eclampsia, hypertension, infections, anaemia, haemorrhage, obstructed labour, duration of labour, caesarean section
- Maternal mortality

SYSTEMATIC REVIEWS/TRIALS EXCLUDED

- Interventions to stop labour
- Interventions to prolong pregnancy after preterm labour
- Interventions that were not exclusively nutritional (ANC packages, social support)

SEARCH STRATEGY

- Cochrane Database of Systematic Reviews up to issue 2, April 2002 (The Cochrane Library)
- For reviews not updated, the Cochrane Controlled Trials Register (CCTR) and Medline were searched up to July 2002.
- Trials identified were considered independently.

SEARCH STRATEGY

- Database of Abstracts of Reviews of Effectiveness (DARE)
- Electronic search of the CCTR for nutritional interventions which have not been reviewed
- Authors of the systematic reviews and trials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DEPARTMENT OF REPRODUCTIVE HEALTH AND RESEARCH
WHO/RHR/02.1
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Geneva, 2002
Programa Especial PNUD/FNUAP/OMS/Banco Mundial de Investigaciones, Desarrollo y Formación de Investigadores en Reproducción Humana
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Ginebra, 2002

INCLUDED IN THE ANALYSES

- 15 systematic reviews
- 69 randomised trials included in the systematic reviews
- 14 randomised trials not included in systematic reviews: fish oil (4) zinc (5), vitamin A-beta carotene (4), vitamins E and C (1).

PRE-ECLAMPSIA

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Nutritional advice	1 (4)	136	0.89 (0.42 - 1.88)
Balanced protein/energy	3 (13)	516	1.20 (0.77 - 1.89)
Isocaloric balanced protein	1 (3)	782	1.00 (0.57 - 1.75)
Energy/ protein restriction	2 (3)	284	1.13 (0.59 - 2.18)
Salt restriction	2 (2)	603	1.11 (0.46 - 2.66)

PREECLAMPSIA

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	6 (6)	6307	0.79 (0.65 – 0.94)
Calcium (high risk)	5 (5)	587	0.21 (0.11 – 0.39)
Calcium (adequate intake)	4 (4)	5022	0.86 (0.71 - 1.05)
Calcium (low intake)	6 (6)	1842	0.32 (0.21 – 0.49)

PRE-ECLAMPSIA

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Magnesium	**2 (7)**	**474**	**0.87 (0.57 - 1.32)**
Fish Oil*	**2 (2)**	**5021**	**0.70 (0.55 - 0.90)**
Vitamins C and E	**1 (-)**	**283**	**0.46 (0.24 - 0.91)**

* New trials have been published after the last update of the Cochrane review

NEW FISH OIL TRIALS: PRE-ECLAMPSIA

		Total women	RR 95%CI
Salvig 1996	Fish oil vs. no treatment	397	0.16* (0.01 - 4.02)
Onwude 1995	Fish oil vs. placebo	232	0.88 (0.46 - 1.65)
Olsen 2000 (EARL-PIH trial)	Fish oil vs. olive oil in women with previous PIH	321	0.72 (0.35 - 1.49)

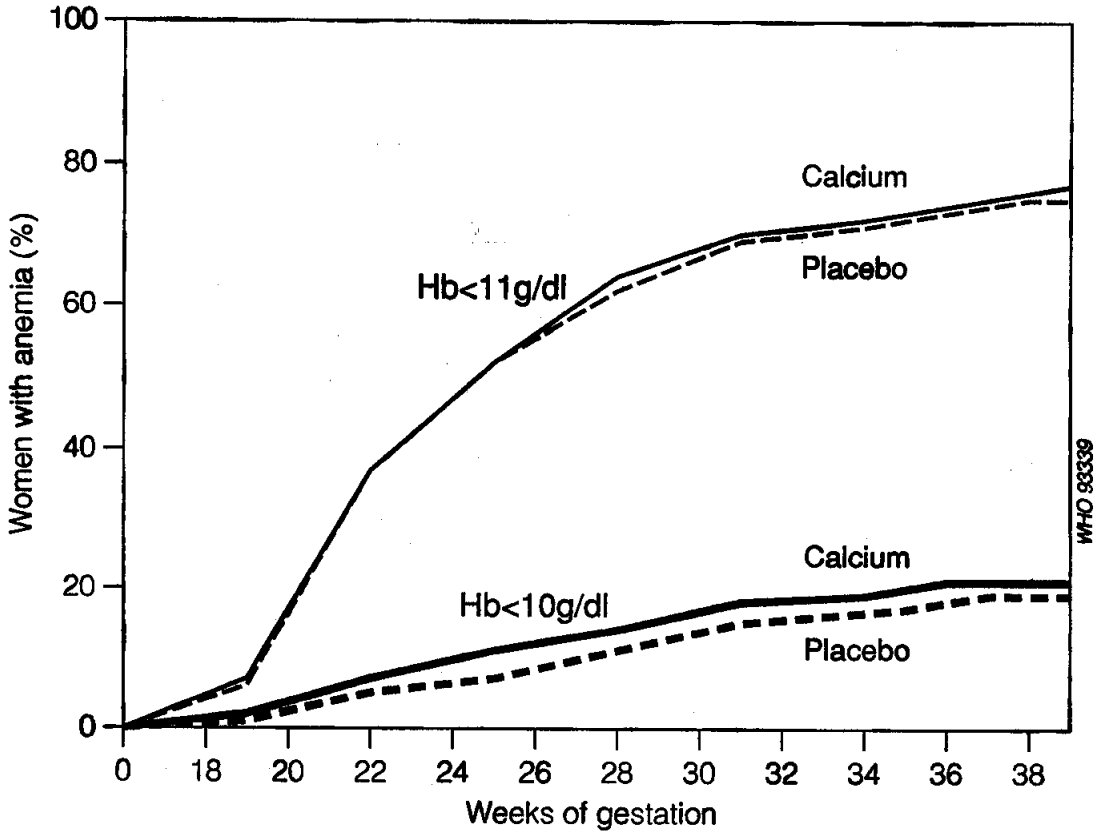
* Expt. = 0/266 Placebo = 1/131

ANAEMIA OR HAEMORRHAGE

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Iron	12 (20)	1802	0.18 (0.13 – 0.24)
Folate	6 (21)	3114	0.72 (0.66 – 0.80)
Iron and folate	6 (8)	1135	0.22 (0.15 - 0.33)
Magnesium	2 (7)	942	0.38 (0.16 – 0.90)
Vitamin A	3 (5)	813	0.91 (0.80 – 1.04)

RATE OF SEVERE POSTPARTUM ANAEMIA (HB< 90 G/L) WHO ANC TRIAL 2001 - ARGENTINA

	New ANC Model % Women	Standard ANC Model % Women
Women supplemented	85.5	20.6
Severe post partum anaemia	8.8	13.3

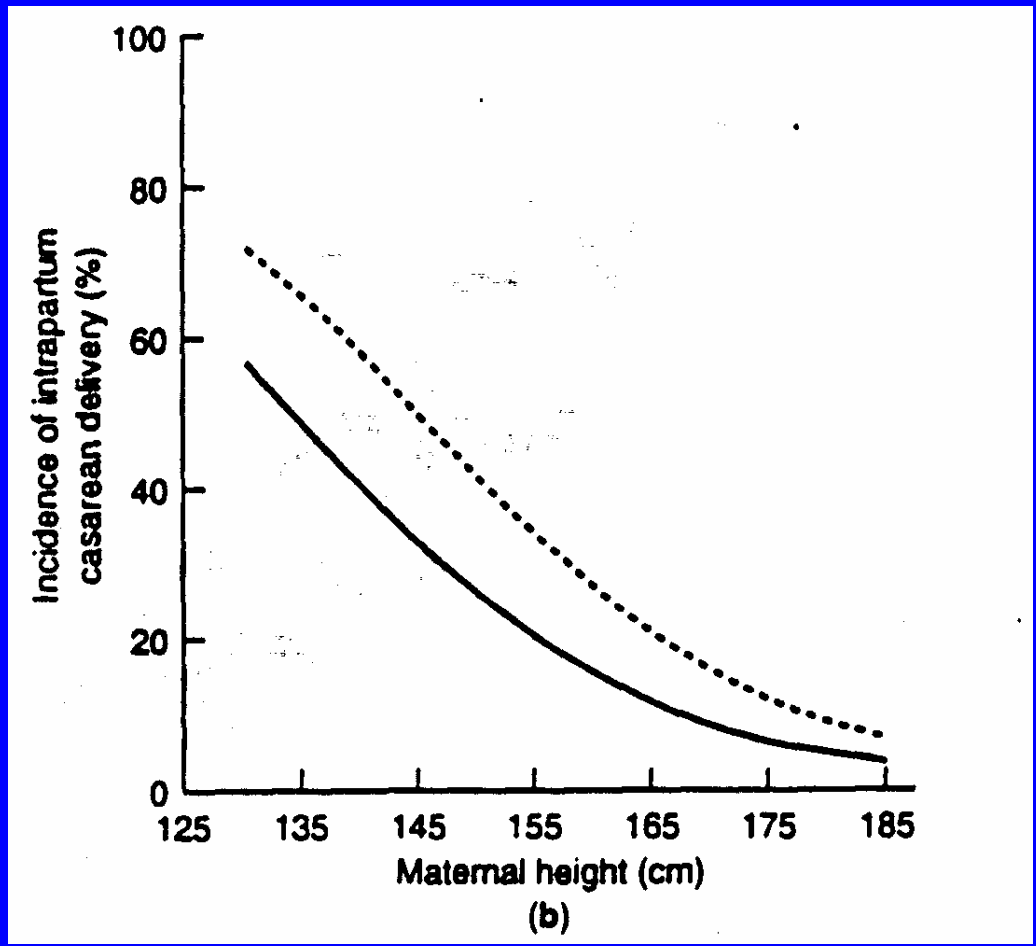


Percentage of women in the calcium and placebo groups in whom hemoglobin values were < 10g/dl or < 11g/dl

OBSTRUCTED LABOUR/CAESAREAN SECTION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Salt restriction	1 (2)	361	0.75 (0.44 – 1.27)
Iron (routine vs. selective)	1 (1)	4052	1.33 (1.03 – 1.70)
Iron (anemia treatment)	1 (2)	100	1.25 (0.36 - 4.38)
Iron and folic acid	2 (8)	104	0.19 (0.02 – 1.45)
Folate	2 (21)	237	0.57 (0.26 – 1.24)
Zinc	3 (7)	1747	0.71 (0.52 – 0.97)

CAESAREAN SECTION AND MATERNAL HEIGHT



Nulliparous women with (……) or without (_____) perinatal distress .BJOG 2001

VITAMIN A AND MATERNAL MORTALITY IN NEPAL (West et al, 1999)

Cause	Placebo (N=7241)	Vitamin A (N= 7747)	Beta carotene (N=7201)
Obstetric	1.00	0.88 (0.42-1.81)	0.56 (0.24-1.31)
Infection	1.00	0.94 (0.42-2.05)	0.60 (0.24-1.51)
Injury	1.00	0	0.20 (0.02-2.32)
Miscellaneous	1.00	0.14 (0.03-0.76)	0.38 (0.13-1.21)
Overall	1.00	0.60 (0.37-0.97)	0.51 (0.30-0.86)

PRETERM DELIVERY

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Nutritional advice	1 (4)	547	0.45 (0.22 - 0.92)
Balanced protein/energy	5 (13)	2436	0.83 (0.65 - 1.06)
Isocaloric balanced protein	1 (3)	782	1.05 (0.69 - 1.70)
Energy/protein restriction	1 (3)	182	0.50 (0.09 - 2.66)
High protein	1 (2)	505	1.14 (0.83 - 1.56)
Salt restriction	1 (2)	242	1.08 (0.46 - 2.56)

PRETERM DELIVERY

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium	9 (11)	6671	0.95 (0.82 - 1.10)
Iron	1 (20)	2694	1.40 (0.94 - 2.09)
Folate	4 (21)	1425	1.03 (0.71 - 1.49)
Magnesium	5 (7)	2275	0.73 (0.57 - 0.94)
Fish oil*	2 (3)	5017	0.83 (0.75 - 0.92)
Zinc*	5 (7)	2539	0.74 (0.56 - 0.98)

* New trials have been published after the last update of the Cochrane review

NEW FISH OIL TRIALS: PRETERM DELIVERY

		Total Women	RR 95%CI
Bulstra-Ramakes 1994	Fish oil vs. placebo	**63**	**0.77 (0.35 - 1.70)**
Onwude 1995	Fish oil vs. placebo	**232**	**0.16 (0.66 - 2.05)**
Olsen 2000 (EARL-PD trial)	Fish oil vs. olive oil in women with previous PTD	**228**	**0.64 (0.41- 0.99)**

NEW ZINC TRIALS: PRETERM DELIVERY

	INTERVENTION	Total Women	RR 95%CI
Caulfield 1999	Zinc (15 mg/day) plus iron plus folate vs. iron plus folate	1016	0.92 (0.56- 1.51)
Osendarp 2000	Zinc (30 mg/day) vs. placebo	410	1.11 (0.72 -1.72)
Merialdi 2001	Zinc (25 mg/day) plus iron plus folate vs. iron plus folate	217	1.54 (0.57 - 4.18)

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRE-ECLAMPSIA

	Practice	Research
Nutritional advice	Not recommended	Not needed
Balanced protein/energy	Not recommended	Not needed
Isocaloric balanced protein	Not recommended	Not needed
Energy/protein restriction	Not recommended	Not needed
Salt restriction	Not recommended	Not needed

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRE-ECLAMPSIA

	Practice	Research
Calcium	**Not recommended**	**Possibly beneficial** for women at high risk RR=0.21 (0.11-0.39) and with low baseline intake RR= 0.32 (0.21-0.49); RCT in progress
Folate	**Not recommended**	**Not needed**
Iron and folate	**Not recommended**	**Not needed**
Magnesium	**Not recommended**	**Not needed**
Fish oil	**Not recommended**	**Needed?** data from low quality studies RR= 0.70 (0.55-0.90) and heterogeneous results in new trials

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRE-ECLAMPSIA

	Practice	Research
Zinc	**Not recommended**	**Not needed**
Vitamins C and E	**Not recommended**	RCT in preparation (data from one RCT in high risk, non deficient women RR= 0.46 0.24-0.91)
Vitamin A	**No data**	**Not needed**
Multinutrients	**Data not available yet**	**RCT completed**

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: ANAEMIA OR HAEMORRHAGE

	Practice	Research
Iron and folate	**Recommended** Very effective intervention	**Need to complete a systematic review of daily vs. weekly supplementation**
Magnesium	**Not recommended**	**Any future trial should include antepartum hemorrhage as primary outcome**
Zinc	**Not recommended**	**Not needed**
Vitamin A	**Not recommended**	**Not needed**

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: INFECTION

	Practice	Research
Zinc	Not recommended	Not needed
Vitamin A	Vitamin A Not recommended, beta carotene effective in reducing death due to infection	New systematic review to be published soon. Update is needed before any new trial

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: OBSTRUCTED LABOUR/CAESAREAN SECTION/DURATION OF LABOUR

	Practice	Research
Balanced protein/ energy	Not recommended	Not needed
Calcium	Not recommended	Not needed
Iron and folate	Not recommended	Not needed
Magnesium	Not recommended	Not needed
Zinc	Not recommended	Any future randomized trial should include rate of caesarean section and/or duration of labour as an outcome

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRETERM DELIVERY

	Practice	Research
Nutritional advice	Not recommended	Promising intervention
Balanced protein/energy	Not recommended	Not needed
Isocaloric balanced protein	Not recommended	Not needed
Energy/protein restriction	Not recommended	Not needed

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRETERM DELIVERY

	Practice	Research
High protein	Not recommended	Not needed
Salt restriction	Not recommended	Not needed
Calcium	Not recommended	Stratified analysis in the new trail by risk level and age (teenagers)
Iron	Not recommended	Not needed
Folate	Not recommended	Not needed

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: PRETERM DELIVERY

	Practice	Research
Iron and folate	Not recommended	Not needed
Magnesium	Not recommended	Needed Promising intervention
Fish oil	Not recommended	Needed Promising intervention
Zinc	Not recommended	Needed Promising intervention

Pregnancy and Childbirth Trials in the *Cochrane Library, 2000*

	N = 9014	%
PPH	45	0.5
Pre-eclampsia	156	1.7
IUGR/SGA	111	1.2
Pre-term delivery	1203	13.3

Global Programme to Conquer Preeclampsia / Eclampsia

Department of Reproductive Health and Research,
World Health Organization and the Global Preeclampsia/
Eclampsia Collaboration

2002

NEW FISH OIL TRIALS: HYPERTENSION

	INTERVENTION	Total Women	RR 95%CI
Salvig 1996	Fish oil vs. no treatment	397	1.97 (0.42 - 9.14)
Bulstra-Ramakes 1994	Fish oil vs. placebo	63	1.66 (0.75 - 3.66)
Onwude 1995	Fish oil vs. placebo	232	1.14 (0.78 - 1.67)
Olsen 2000 (EARL-PIH trial)	Fish oil vs. olive oil in women with previous PIH	350	0.99 (0.73 - 1.33)

MATERNAL INFECTION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Zinc	1 (7)	487	1.22 (0.79 – 1.90)

OBSTRUCTED LABOUR/CAESAREAN SECTION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	4 (6)	6080	0.94 (0.84 – 1.06)
Calcium (high risk)	2 (5)	252	0.77 (0.43 – 1.37)
Calcium (adequate intake)	3 (4)	4981	0.95 (0.84 - 1.07)
Calcium (low intake)	3 (6)	1351	0.86 (0.64 – 1.18)

DURATION OF LABOUR

	Trials with outcome reported (trials in systematic review)	Total women	Mean difference (hours) 95%CI
Balanced energy/ protein	1 (6)	345	-0.1 (-1.20 – 0.90)
Magnesium	1 (7)	568	0 (0.52 – 0.97)

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: HYPERTENSION

Nutrient	Practice	Research
Energy protein restriction	**Not recommended**	**Not needed**
Salt restriction	**Not recommended**	**Not needed**
Calcium	**Not recommended**	**RCT in progress** Possibly beneficial for women at high risk RR=0.45 (0.31-0.66) and with low baseline intake RR= 0.49 (0.38-0.62)
Folate	**Not recommended**	**Not needed**

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: HYPERTENSION

	Practice	Research
Iron and folate	Not recommended	Not needed
Fish oil	Not recommended	Not needed
Zinc	Not recommended	Not needed
Vitamins E and C	Not recommended	Not needed (RCT in different populations)
Multinutrients	Data not available yet	RCT completed

OVERVIEW

- Epidemiological associations versus impact of pragmatic interventions
- Timing of the “insult” and different fetal organ growth patterns
- Timing and location of nutrient deposition in the mother and fetal growth

OVERVIEW

- Duration and “dose”of supplementation
- Pharmacological versus nutritional effect
- Intervention specific outcomes versus overall mortality/birth weight outcomes
- Heterogeneity of outcomes and their causes

HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Energy/protein restriction	3 (3)	384	0.97 (0.75 - 1.26)
Salt restriction	2 (1)	242	0.97 (0.49 - 1.94)

HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	6 (6)	6307	0.84 (0.76 – 0.92)
Calcium (high risk)	5 (5)	587	0.21 (0.11 – 0.39)
Calcium (adequate intake)	4 (4)	5022	0.86 (0.71 - 1.05)
Calcium (low intake)	6 (6)	1842	0.32 (0.21 – 0.49)

HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Iron and folate	2 (8)	87	1.15 (0.41 – 3.81)
Folate	2 (21)	696	1.26 (0.90 – 1.76)
Fish Oil*	2 (2)	5108	0.96 (0.86 - 1.07)
Zinc*	4 (7)	1962	0.87 (0.65 – 1.15)
Vitamins E and C	1 (-)	283	1.24 (0.62 – 2.48)