IMPAIRED FETAL GROWTH

Mario Merialdi

Office X 39

Phone 022 7913387

merialdim@who.int

Historical perspective

Public health importance

Impaired fetal growth is:

- prevalent in developing countries
- is associated with short and long term negative outcome in fetuses, infants and children
- may be associated with development of disease in adult life

Today’s approach

- Assessment fetal growth in populations
- Prevalence in different countries
- Consequences for health
- Interventions to prevent impaired fetal growth
- Further research

Characteristics of the fetus with IUGR

- Asymmetry in the dimensions of head and abdomen
- Reduced amniotic fluid
- Small placenta

Pathophysiology of impaired fetal growth

Placental insufficiency:

- Reduced transfer of nutrients
- Fetal hypoperfusion

Consequences of IUGR

- Higher perinatal morbidity and mortality
- Higher infant mortality and childhood morbidity
- Poor cognitive development and neurologic impairment
- Increased risk in adulthood of cardiovascular disease, high blood pressure, obstructive lung disease, diabetes, high cholesterol and renal damage.

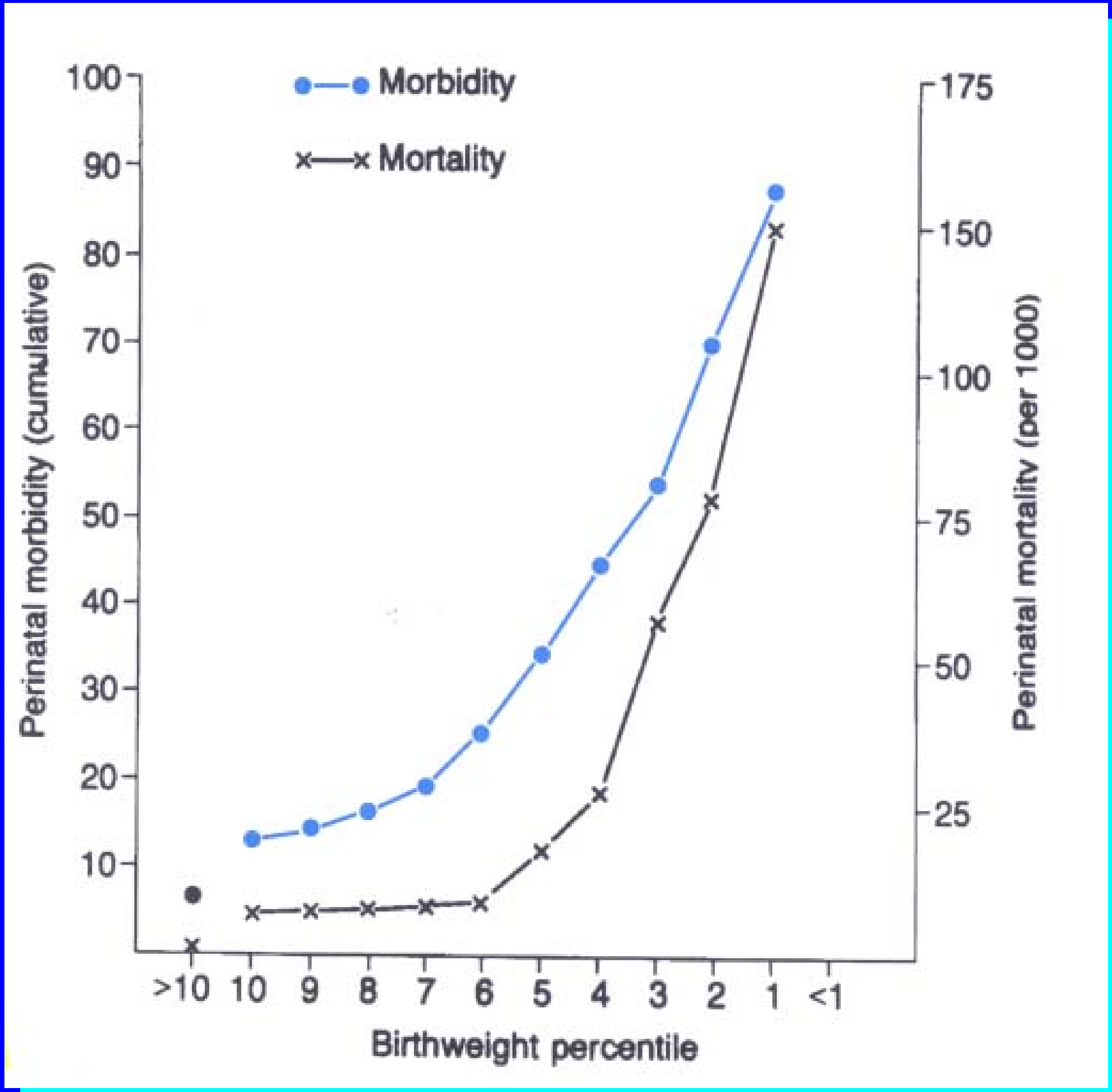
Population based Perinatal mortality according to birth weight percentile:

Chile, all 262681 deliveries in 1999

Edad gestacional (semanas)	<p5	<p10	p10-90	Ratio <p10 / p10-90
22-25	1000	1000	679	1.5
26-29	616	519	288	1.8
30-33	372	357	116	3.1
34-36	168	128	30	4.3
37-40	19	12	2	6.0
41-43	14	10	2	5.0
Total	**110**	**62**	**3**	**20.7**

Gonzalez R. personal communication (2003)

IUGR and mortality



Assessment of fetal growth

- Retrospective assessment using anthropometric measures of size at birth (birth weight)
- Prospective assessment by serial clinical evaluations (uterine height, ultrasound measurements of fetal anatomical parameters)

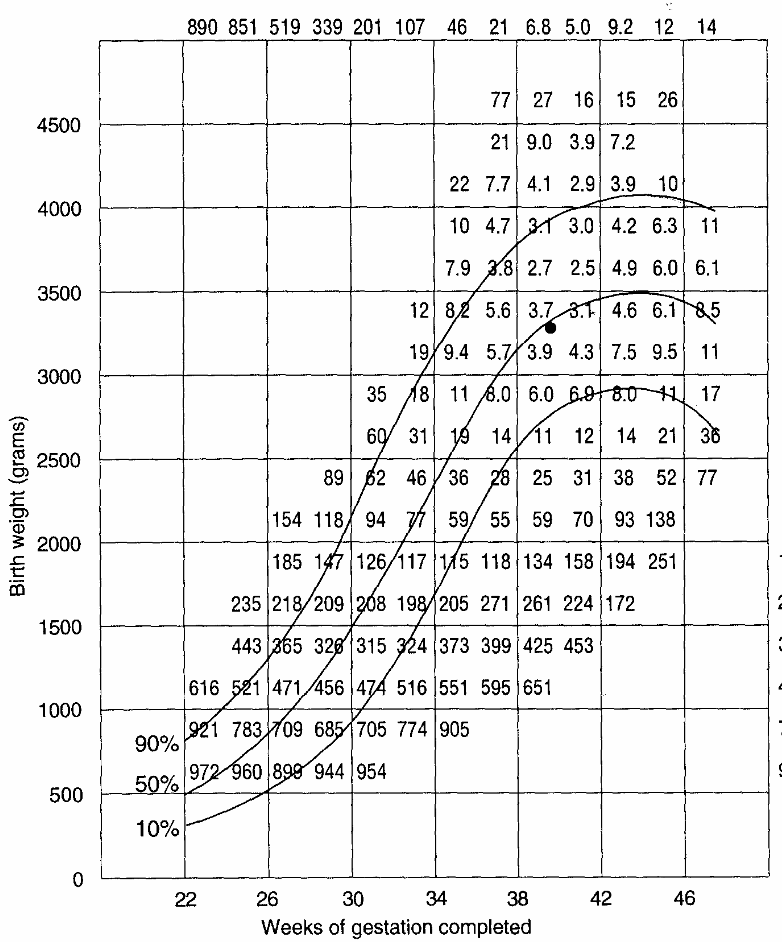
Classification of fetal growth based on birth weight

- Low birth weight: < 2500 grams (does not differentiate between infants born small at term or infants small because they are preterm)
- Small for gestational age: birth weight below the the 10th percentile for a given gestational age (may erroneously categorize some normal growth newborns as growth impaired).

Figure 18

Birth weight percentiles and perinatal mortality rates (per 1000) for single female births[a]

Note: The mean birth weight-gestational age combination is marked with a black dot. Down the right-hand side are the birth-weight-specific rates for all gestational ages, and across the top are the gestational-age-specific rates for all birth weights. The birth-weight/gestational-age-specific mortality rates, computed on the basis of 2-week gestation and 250-g weight intervals, are plotted within the square corresponding to the appropriate intersection of the birth-weight/gestational-age grid. For example, the perinatal mortality rate for infants weighing between 3251 and 3500 g and of 40 and 41 completed weeks of gestation is 3.1. The perinatal mortality rate for the birth-weight group 3251-3500 g for all gestational ages is 4.0 per 1000, and the perinatal mortality rate for the 40- to 41-week gestational age group for all birth weights is 5.0.



[a] Reproduced from reference *84* with permission from the American College of Obstetricians and Gynecologists.

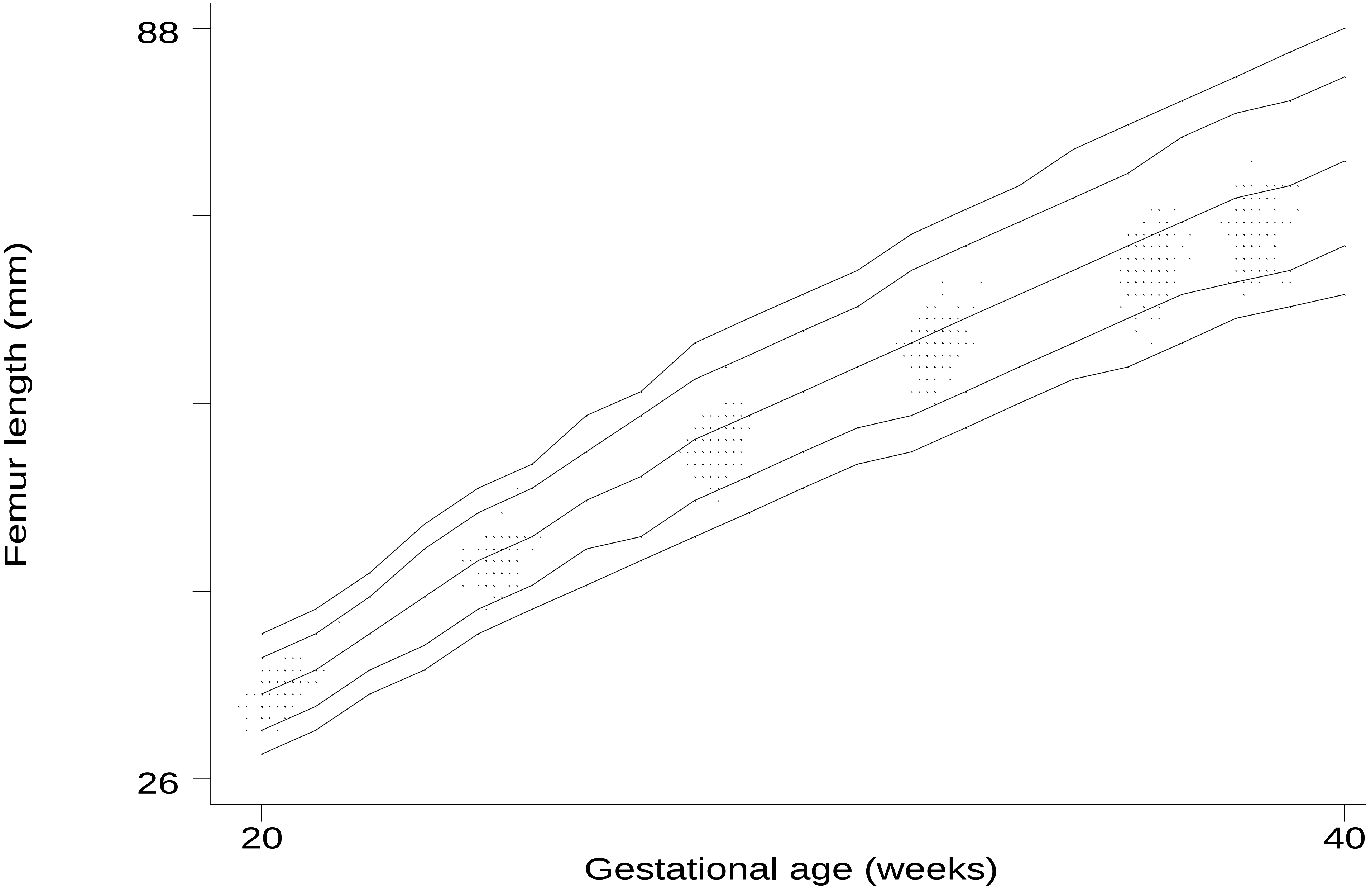
Reference data based on birth weight

The method is relatively easy to implement but has limitations:

- the cross sectional approach (data collected at birth from infants of different ages) may not reflect the longitudinal growth of fetuses of the same ages
- inaccuracies of estimation of gestational age at delivery affect interpretation
- pathological processes that could affect the size of infants born early in gestation

Ultrasound measurements

- Large coefficient of variation associated with estimations of fetal weight
- Margin of error in measuring individual anatomical parameters is contained
- Allow for both cross sectional and longitudinal assessment (Individualized Growth Assessment)



88
26
Femur length (mm)
20
40
Gestational age (weeks)

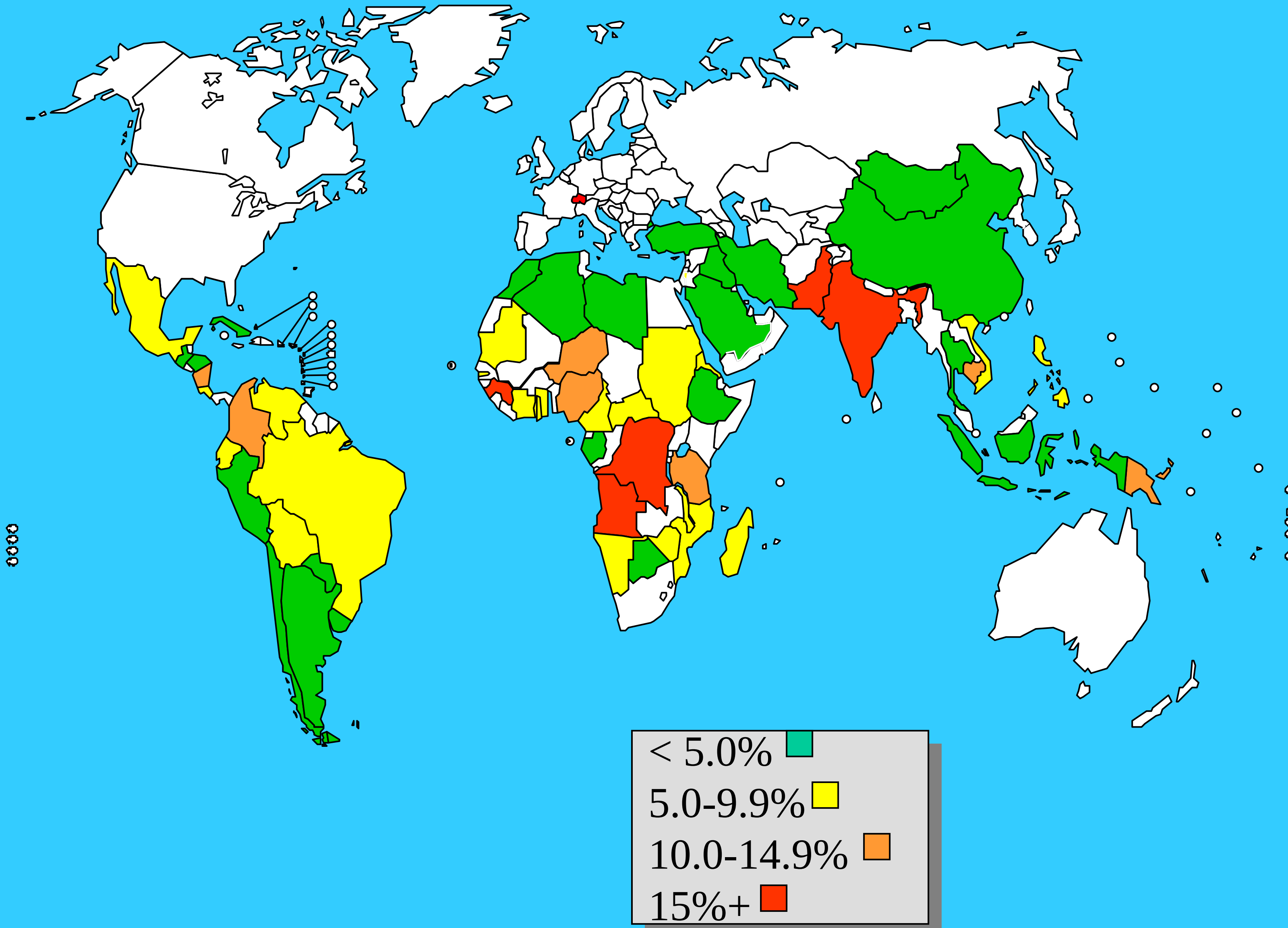
Internationally recommended cut-off levels for triggering public health action

- IUGR > 20%
- LBW > 15%

Estimates of impaired fetal growth in developing countries

Indicator	Source	%	Estimated total number of newborns affected per year
IUGR-LBW (<2500 g; >= 37 wks)	LBW rates from WHO data bank (1992) and regression model (Villar, 1994)	11	13,699,000
LBW < 2500 g all gestaional ages	LBW rates from who data bank (1982)	16.4	20,423,000
IUGR < 10 percentile all gestational ages	WHO collaborative study on maternal anthropometry and pregnancy outcomes (1995)	23.8	29,639,000

Global estimates of IUGR-LBW in developing countries (1985-1995)



IUGR-LBW

- Estimates should be viewed as conservative
- 75% of all affected newborns are born in Asia
- Rates are 6 times larger than in developed countries
- We need to improve:

  - quality and availability of birth weight data

  - assessment of gestational age

Interventions to prevent or treat impaired fetal growth

Care and advice during pregnancy

Intervention	# trials	Participants (E+C)	Outcome	OR (95% CI)
Continuity of caregivers	2	908+907	Term - LBW	0.94 (0.65, 1.36)
Social support for women at risk	8	3564 + 3477	Term - LBW	0.97 (0.84, 1.13)
Own case-notes	2	276 +276	Term - LBW	0.67 (0.35, 1.30)
Stop smoking	5	2950 + 2771	Term - LBW	0.80 (0.65, 0.98)
Nutritional advice	1	265 + 250	SGA	1.00 (0.48, 2.08)

Antimalarial chemoprophylaxis

Intervention	# trials	Participants (E+C)	Outcome	Mean difference (95% CI)
All parities	5	1453 + 1616	MBW	23g (-13, 59)
Multigravida	2	342 + 362	MBW	65g (4, 125)
Primigravida	4	295 + 340	MBW	112g (41, 183)

Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Balanced protein energy	6	2147+2123	SGA	0.68 (0.57, 0.80)
Isocaloric balanced protein	1	391 + 391	SGA	1.35 (1.12, 1.61)
High protein	1	249 +256	SGA	1.58 (1.03, 2.51)
Salt restriction	1	110 + 132	SGA	1.50 (0.73, 3.07)
Salt restriction	1	184 + 177	LBW	0.84 (0.42, 1.67)

Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Calcium	1	97 +93	SGA	0.72 (0.26, 1.99)
Calcium	7	3230 + 3261	LBW	0.83 (0.71, 0.98)
Folate	5	754 +734	LBW	0.75 (0.50, 1.12)
Iron selective vs. routine	1	50 + 50	SGA	1.60 (0.56, 4.56)

Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Magnesium	3	865 + 876	SGA	0.70 (0.53, 0.93)
Magnesium	4	968 + 986	LBW	0.67 (0.46, 0.96)
Zinc	3	909 + 931	SGA	0.90 (0.64, 1.28)
Zinc	5	750 + 722	LBW	0.77 (0.56, 1.06)
Vitamin D	1	67 + 59	SGA	0.54 (0.26, 1.10)

- Most interventions aimed to prevent or treat impaired fetal growth do not show significant effects on short term perinatal outcomes

Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

Epidemiological associations versus effectiveness of pragmatic interventions

Timing of the ”insult” versus different fetal organ growth patterns

Timing and site of nutrient deposition in the mothers and the effect on fetal growth

Interpretation of the results of randomized clinical trials of maternal nutritional interventions

Intervention specific outcomes versus morbidity/mortality/birth weight outcomes

Length and “dose” of nutritional supplementation

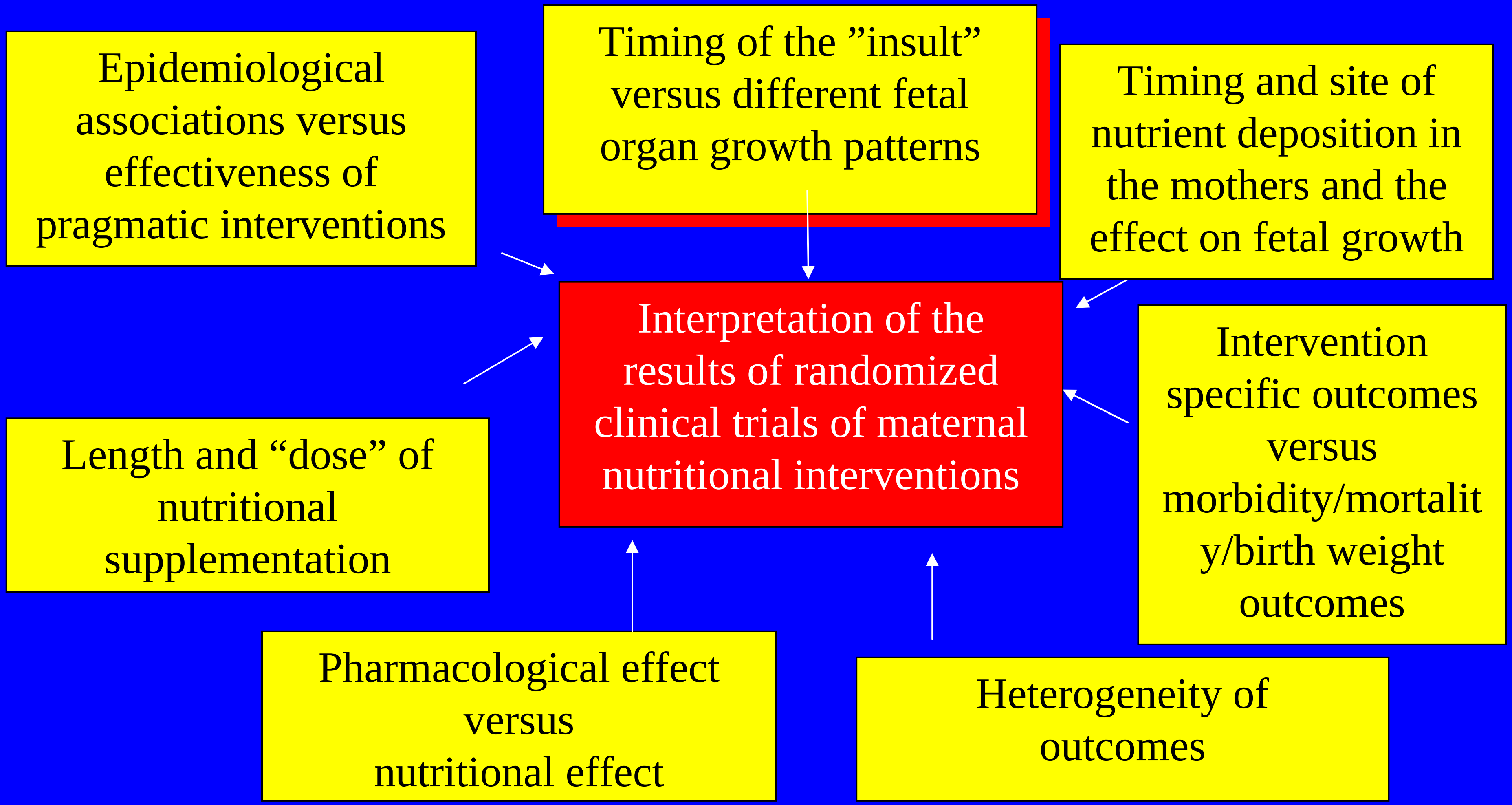
Pharmacological effect versus nutritional effect

Heterogeneity of outcomes

Epidemiological association vs. effectiveness of pragmatic interventions

- Results from observational studies or uncontrolled observations are likely to be confounded by the effect of population characteristics
- Women from disadvantaged populations are more at risk for nutritional deficiencies as well as for pregnancy complications
- Intervention groups may be better off and have better outcomes

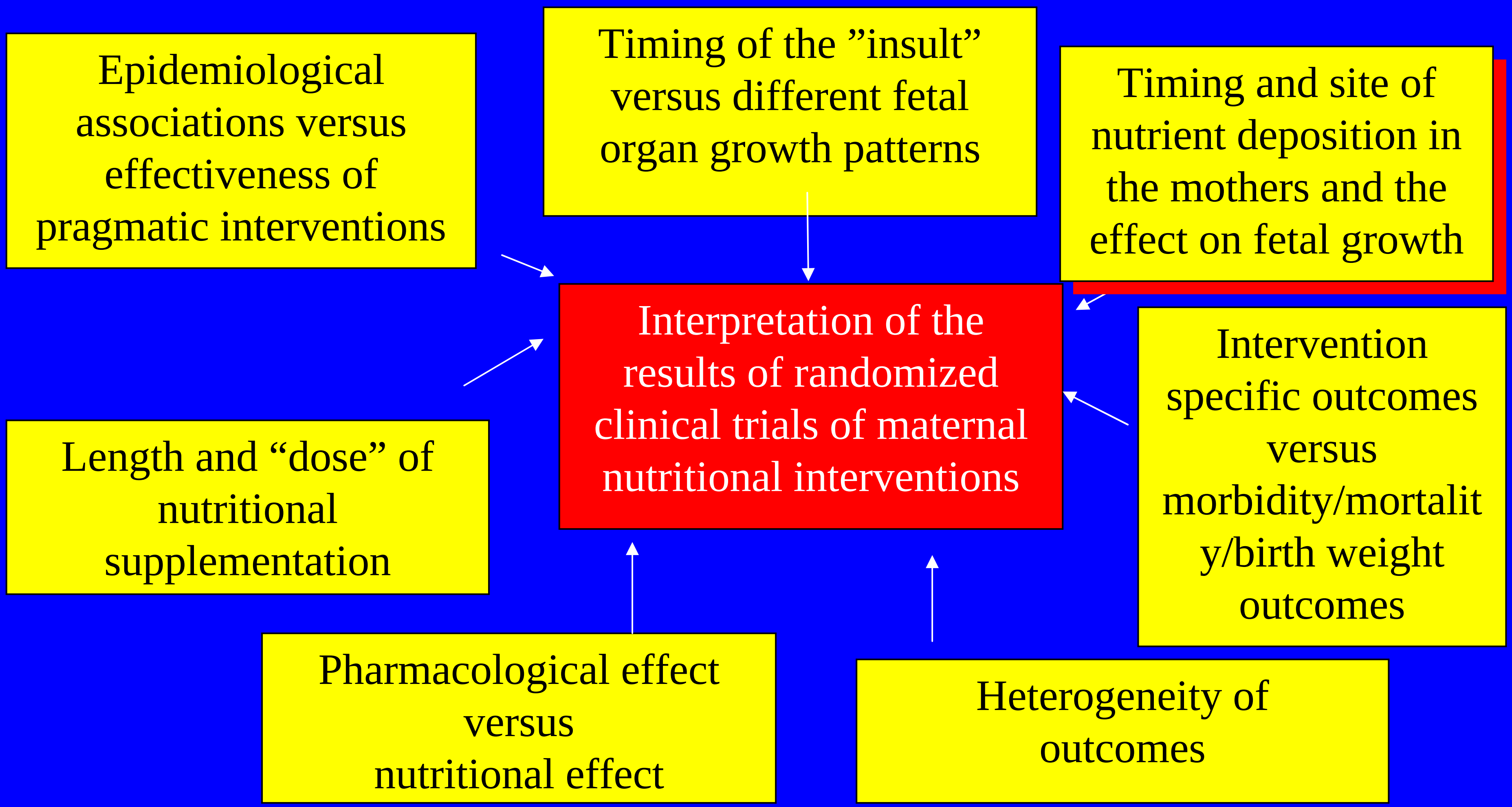
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy



Timing of the insult and different fetal organ growth patterns

- Fetal organs show differential growth patterns and contribute differently to total fetal volume at different gestational ages (eg.: relationship between head and abdomen)
- The effect of a nutritional deficiency or nutritional intervention on a the growth of a fetal organ is likely to be related to the timing of he insult during gestation

Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy



Timing of nutrient deposition in the mother and the effect on fetal growth

- Differential timing of nutrient deposition and its body location may also influence nutrient transfer to the fetus
- Birth weight is associated more with maternal changes in thigh skinfolds and early gestation fat gain than with other body sites or pregnancy times

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Length and amount of nutritional supplementation

- It is unrealistic to assume that chronic undernutrition during two or three decades of life will be overcome, in terms of reproductive performance with only a few months of extra nutrient intake
- Energy supplementation was more effective on birth weight if it was provided for two consecutive pregnancies than during only one pregnancy

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Pharmacological vs. Nutritional effect

- Nutrients can be provided to population with dietary deficiency (nutritional effect) or to population with adequate intake (pharmacological effect)
- Calcium supplementation for the prevention of preeclampsia seems to be effective in low calcium intake women but not in adequate calcium intake women.

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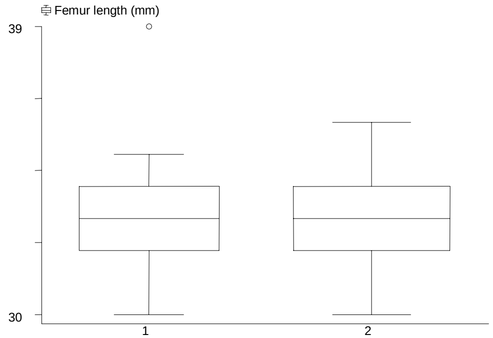
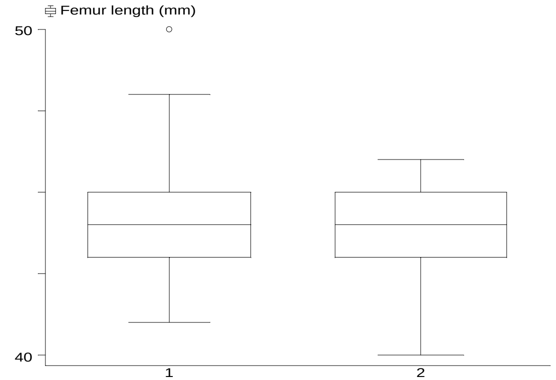
Intervention specific outcomes

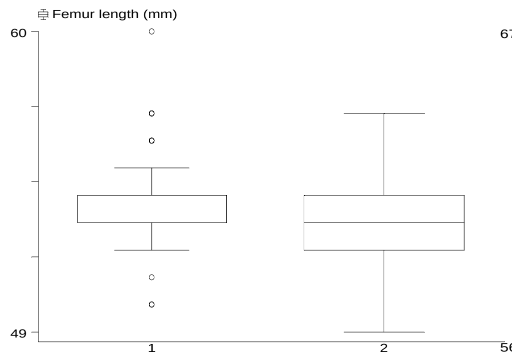
- It is important to identify the most specific outcome in reference to the nutrient being evaluated
- Zinc supplementation did not increased birthweight but had a positive effect on femur length measured by ultrasonography
- “Birth weight may be too crude a marker to to capture the range of all possible uterine exposure and experiences”



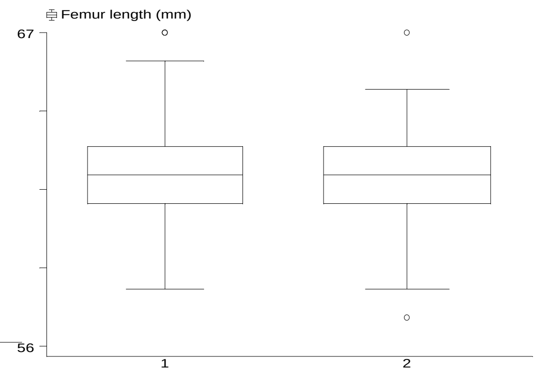
20 weeks



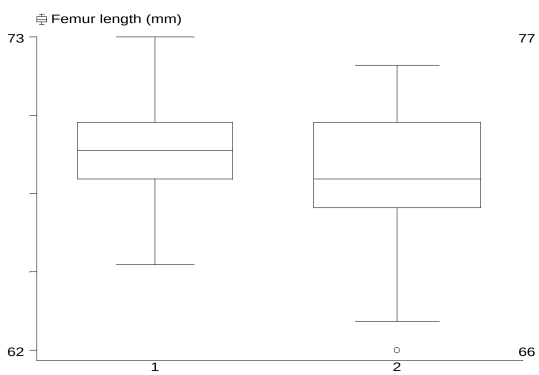
24 weeks



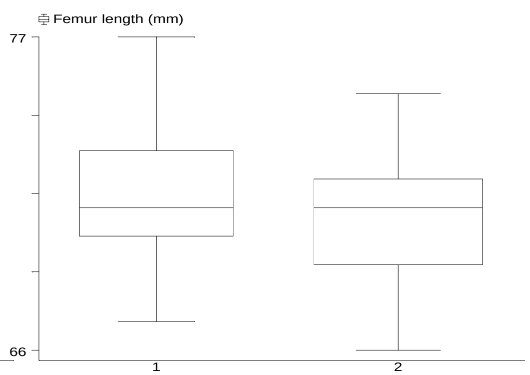
28 weeks



32 weeks



36 weeks



38 weeks

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Heterogeneity of outcomes

Heterogeneity of outcomes

- Low birth weight and small for gestational age includes conditions with different aetiologies.
- These outcomes may be too comprehensive to be significantly affected by a single nutritional intervention

Further research

- Extend the duration of nutritional supplementation interventions and follow up (Barker hypothesis)
- Identify new outcomes and evaluate their biological and clinical relevance
- Evaluate combinations of interventions
- Develop mechanistic hypotheses
- Identify the determinants of fetal growth (genetics vs. environment) and develop standards of fetal growth for international applications
- Individualised Growth Assessment

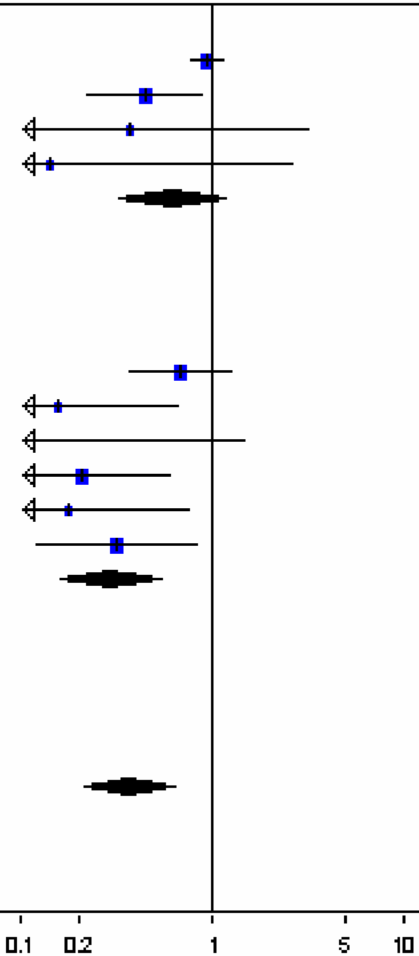
Individualised Growth Assessment

- Each fetus serves as its own control
- The expected normal range of growth is determined by an equation using measurements from two fetal biometry assessments performed during the second trimester
- Takes into account the fetal growth potential of each individual fetus

Review: Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems
Comparison: 02 Routine calcium supplementation in pregnancy by baseline dietary calcium
Outcome: 02 Pre-eclampsia

Study	Treatment	Control	Weight %	Relative Risk (Random) 95% CI
01 Adequate calcium diet				
CPEP 1997	158 / 2163	168 / 2173	19.2	0.94 [0.77, 1.16]
Crowther 1999	10 / 227	23 / 229	14.7	0.44 [0.21, 0.90]
Villar 1987	1 / 25	3 / 27	4.7	0.36 [0.04, 3.24]
Villar 1990	0 / 90	3 / 88	2.9	0.14 [0.01, 2.67]
Subtotal (95% CI)	169 / 2505	197 / 2517	41.5	0.62 [0.32, 1.20]
Test for heterogeneity chi-square=6.20 df=3 p=0.1024				
Test for overall effect Z=-1.43 p=0.15				
03 Low calcium diet				
Belizan 1991	15 / 579	23 / 588	15.5	0.66 [0.35, 1.26]
L-Jaramillo 1989	2 / 55	12 / 51	8.3	0.15 [0.04, 0.66]
L-Jaramillo 1990	0 / 22	8 / 34	3.2	0.09 [0.01, 1.48]
L-Jaramillo 1997	4 / 125	21 / 135	11.5	0.21 [0.07, 0.58]
Purwar 1996	2 / 97	11 / 93	8.0	0.17 [0.04, 0.77]
S-Ramos 1994	4 / 29	15 / 34	12.0	0.31 [0.12, 0.84]
Subtotal (95% CI)	27 / 907	90 / 935	58.5	0.29 [0.16, 0.54]
Test for heterogeneity chi-square=8.04 df=5 p=0.1540				
Test for overall effect Z=-4.00 p=0.00				
Total (95% CI)	196/ 3412	287/ 3452	100.0	0.37 [0.21, 0.64]
Test for heterogeneity chi-square=28.67 df=9 p=0.0007				
Test for overall effect Z=-3.57 p=0.00				

Relative Risk (Random) 95% CI



Reduced transfer of nutrients

- Abnormalities of the placenta lead to increased resistance of blood flow in the placenta
- Increased resistance determines a reduction of flow through the placenta
- the fetus reacts to a condition of limited supply of nutrients and oxygen by vascular redistribution that spares vital organs (brain, myocardium, adrenal glands).