

**MEETING OF ADVISORY GROUP ON
MATERNAL NUTRITION AND
LOW BIRTHWEIGHT**

Geneva, 4 – 6 December 2002





**Meeting of Advisory Group on Maternal Nutrition
and Low Birthweight
Geneva, 4-6 December 2002**

Table of Contents	Page
1. Abstract	1
2. Executive summary	2-6
3. Scope of the report	7
4. Objectives	7
5. Terms of reference	7
6. Format of this report	8
7. Introduction	8-11
7.1 Definition of Low Birthweight	8
7.2 Subtypes of IUGR	8-9
7.3 Long-term sequelae of PTB and IUGR	9
7.4 Prevalence of LWB-IUGR	9-10
7.5 Trends in PTB and LBW in developing countries	10-11
7.6 Discussion points	11
8. WHO global and regional estimates on low birthweight	11-12
9. What is the nature of the evidence and how can we use it?	12-13
9.1 Breadth of the enquiry	12
9.2 Types of evidence and methodological issues	12
9.3 Gaps in the evidence	12-13
9.4 Framework for the development of the strategy (Annex 3)	13
10. What are we trying to achieve – prevention of low birthweight or wider improvement in fetal growth?	13-15
10.1 What outcomes are important?	13
10.2 What is optimal growth?	14
10.3 Measurement of fetal growth	14
10.4 Gestational age	14
10.5 Points of agreement	14-15
11. What determines optimal fetal growth/low birthweight?	15-18
11.1 Determinants of IUGR and PTB	15-17
11.2 Prevention of PTB and IUGR	17
11.3 Discussion points	17-18
11.4 Points of agreement	18

Table of contents (cont'd.)

12. What interventions might be employed to promote fetal growth/prevent low birthweight?	19-22
12.1 Interventions to prevent PTB	19-20
12.2 Interventions to prevent IUGR	20-21
12.3 Other important issues	22
12.4 Discussion points	22
12.5 Points of agreement	22
13. How do issues vary between different settings and populations?	23-27
13.1 Determinants of variations in birthweight	23
13.2 Maternal anthropometry	23-24
13.3 Pregnancy outcome	24
13.4 Variations in risk factors for LBW	25-26
13.5 Discussion points	26-27
13.6 Points of agreement	27
14. What are the possible timescales for action?	27-29
14.1 Evidence from developing countries	27-28
14.2 Inter-generational effects	28
14.3 Should interventions be targeted during pregnancy?	28-29
14.4 Discussion points	29
15. Summary of consensus issues and recommendations to address gaps in the evidence	29-33
15.1 Consensus issues	29-30
15.2 Gaps and recommendations	30-33
References	34
Annex 1 List of participants	35-38
Annex 2 Agenda	39-40
Annex 3 Framework	41-43

1. ABSTRACT

In December 2002, a small, informal advisory group of experts met to discuss the development of a WHO strategy for the prevention of low birthweight (LBW). The group reviewed the evidence on the burden of LBW and interventions to prevent it. It also identified gaps in the evidence base, and made recommendations on further work needed to inform the development of a WHO strategy.

LBW results from preterm birth (PTB), intra-uterine growth retardation (IUGR) or both. LBW has high prevalence in many developing countries and is an important clinical issue in developed countries. LBW is associated with early mortality and morbidity and with adverse long term outcomes. The group agreed that a strategy should address general improvement in fetal growth rather than focusing only on LBW, and that it should be aimed at improving both short and long term outcomes.

There are significant gaps in the knowledge of the determinants of both IUGR and PTB, particularly in developing country settings. Determinants of IUGR include cigarette smoking, low weight gain, low BMI, primiparity, short stature, malaria and pregnancy-induced hypertension. Much less is known about the determinants of PTB. A number of determinants of IUGR and PTB are associated with “upstream” factors such as poverty or lack of maternal education.

Interventions that have been shown to be effective in preventing IUGR are macronutrient food supplementation, counselling to reduce cigarette smoking, malarial prophylaxis in primiparous women, and low dose aspirin in high risk women. In many of these, reductions in rates of LBW or IUGR, or improvements in mean birthweight have been relatively modest. Evaluation of public health food supplementation programmes is awaited. Evidence on prevention of PTB is limited although there is some RCT evidence to suggest that reduction in smoking, treatment of bacteruria, use of fish oil supplements and cerclage in women with cervical incompetence are effective. The timing of interventions (pre- or during pregnancy), and the extent to which they should be conditioned on maternal size is not yet known. IUGR and PTB are both multifactorial in etiology, and it is unlikely that interventions directed at single risk factors will have a major impact on their prevention at population level.

There are a number of important gaps in the evidence. These include: lack of data on prevalence and burden of LBW, IUGR, and PTB, particularly in developing countries; relation of LBW, IUGR and PTB to early and long term outcomes; etiology of PTB and IUGR; interventions at a population level; cost effectiveness of interventions.

2. EXECUTIVE SUMMARY

Scope of the report

1. The report describes a meeting of an informal advisory group of experts which took place in Geneva in December 2002. The meeting was held to inform the development of a WHO strategy for the prevention of low birthweight (LBW).
2. This executive summary integrates the proceedings and conclusions of the meeting. It should be noted that not all relevant evidence was presented at the meeting, and that there was debate and discussion on many of the issues. However, there were many areas of general agreement, together with identification of gaps in the available evidence. These are presented in this summary and the full report. The full report gives greater detail on the proceedings, and on the discussion and debate.

Objectives of the meeting

- 3.1. To review the burden of LBW.
- 3.2. To review the evidence for effective interventions to prevent LBW.
- 3.3. To identify priorities for action and make recommendations for work that needs to be undertaken to inform the expert consultation on LBW.

Terms of reference

- 4.1. The group will act as a source of scientific advice to assist WHO and its partners in developing a strategy to improve fetal growth and/or prevent LBW.
- 4.2. The group will identify scientific questions which need to be answered to inform the strategy, and advise on the state of the evidence base which addresses those questions, specifically what is known (and how that knowledge has been collated), what is not known, and how gaps in knowledge might be addressed.
- 4.3. The group will advise on priorities for action to improve fetal growth and/or prevent LBW.

Burden of low birthweight

5. LBW results from intra-uterine growth retardation (IUGR), preterm birth (PTB) or both. LBW is defined as weighing less than 2500 grams at birth and PTB as a gestational age at delivery of less than 37 completed weeks. Definitions of IUGR vary. Only a proportion of babies with PTB or LBW will suffer from IUGR.
6. Subtypes of IUGR have been identified with suggestions that the timing of growth restriction in utero differs between sub-types. However, the difference may also be due to the severity of the restriction.

7. PTB and IUGR are associated with early mortality and morbidity and with adverse long term outcomes. In PTB these include neurological, pulmonary and ophthalmic disorders. In IUGR they include growth and neurological disorders, and increased risk of adult cardiovascular disease.
8. In developing countries, the highest prevalence of LBW is seen in the Indian sub-continent and South Africa. Moderately high rates are seen in parts of Latin America and other parts of Africa, whereas low rates are seen in China and Chile. In general, better data are needed from developing countries.
9. In developed countries, rates of LBW are lower, but the picture is complicated by the relatively high rates of fertility treatment. Rates of PTB have increased over recent decades but there has been a decline in LBW rates, probably due to rising mean birthweight and better obstetric care. Mean birthweight may have risen because of greater maternal BMI and pregnancy weight gain, and reduced maternal smoking.

Nature and uses of the evidence

10. Much of evidence to identify the causes of LBW is observational. Randomised controlled trials (RCTs) are the best type of evidence for assessing interventions, but for population level (“upstream”) interventions, trial designs may not be feasible.
11. Important evidence gaps include: evaluation of community/population level interventions (especially using experimental designs); attributable risk for etiologic factors; cost effectiveness of interventions; and assessment of the burden of ill health associated with LBW across the life course. The lack of evidence from developing countries documenting the extent of LBW, IUGR and PTB and the burden that is associated with them is a major gap.

What are we trying to achieve: prevention of LBW or wider improvement of fetal growth?

12. The group agreed that the aim of preventing LBW was to achieve improvement in a wide range of outcomes across the life course. These outcomes include mortality, morbidity, quality of life, developmental status and health related behaviour. The balance of outcomes which would be achieved early rather than later, and which would be beneficial rather than adverse would also be influential in decision making.
13. Birthweight is a summary of fetal growth. Patterns of fetal growth and body composition of the fetus may be important, but data on these are lacking particularly in developing countries.
14. The relationship between birthweight and early and late outcomes appears to be continuous, with little evidence of threshold effects at either end of the distribution. However, future monitoring may need to take account of the use of thresholds (eg 2500 grams) in the past. The use of the dichotomous measure of LBW has two disadvantages. Firstly, it does not distinguish between PTB and IUGR, and secondly, it does not permit assessment of the entire range of gestation or fetal growth.

15. Optimal birthweight may be different according to the size of the mother, as maternal growth constraint may protect the health of the mother and baby. The differential effect of shifting the birthweight distribution in different populations on maternal and offspring health is unknown.

What determines birthweight?

16. The etiologic fraction is the proportion of the outcome in a given population that can be attributed to a given risk factor. Therefore, it is determined both by the relative risk of the outcome for the risk factor, and the prevalence of the risk factor.
17. In developed countries the major determinants of IUGR are cigarette smoking, low weight gain, low BMI, primiparity and short stature. In developing countries they are low weight gain, low BMI, short stature, malaria and pregnancy-induced hypertension. A substantial proportion of the etiology of IUGR is unknown in both settings. The proportion of women smoking tobacco is increasing in developing countries, and so maternal smoking may become more important in this setting. Similarly, the changing patterns of weight gain and obesity may alter the risks associated with maternal BMI and pregnancy weight gain.
18. Much less is known about the determinants of PTB. In developed countries the major attributable causes are genito-urinary infection, multiple births and pregnancy-induced hypertension, with a significant proportion of the etiologic fraction unexplained. There are insufficient data from developing countries to perform equivalent analyses.
19. A number of the determinants of IUGR and PTB are associated with “upstream” factors such as poverty or lack of maternal education, which have not been assessed as etiologic fractions.
20. Knowledge of the determinants of IUGR and PTB suggests that the optimal time to intervene might be before pregnancy. However, there is insufficient evidence to inform such a decision.

What interventions might be employed to promote fetal growth and/or prevent LBW?

21. Modifiable determinants of IUGR include maternal stature, BMI, age, birth interval (pre-pregnancy), energy and protein intake, weight gain, micronutrient status, smoking/pollution, violence, stress (pregnancy), malaria and other maternal and fetal infections. Interventions that have been shown to be effective in preventing IUGR are macronutrient food supplementation, counselling to reduce cigarette smoking, malarial prophylaxis in primiparous women, and low dose aspirin in high risk women. In many of these, reductions in rates of LBW or IUGR or improvements in mean birthweight have been relatively modest. Trials of multiple micronutrient supplementation are underway.
22. Evidence on the prevention of PTB is limited. There is some evidence from RCTs to suggest that reduction in smoking, treatment of bacteruria, use of fish oil supplements

and cerclage in women with cervical incompetence are effective. Reduction of workload for prevention of PTB is promising but requires evaluation.

23. For both IUGR and PTB much of the evidence of effectiveness comes from research studies in developed countries only. There are significant gaps in evidence from developing countries, for upstream compared to downstream interventions, and for the practicality and cost effectiveness of interventions. Evidence on maternal nutritional supplementation in developing countries has come from research programmes. Evaluation of public health food supplementation programmes is awaited.
24. The optimal timing of interventions is not known, particularly whether interventions should be before or during pregnancy. Similarly, the effect of some interventions on the health of the mother (rather than the baby) is unknown.
25. Inter-generational influences on birthweight may limit the extent to which birthweight distributions can and should be shifted. However, evidence suggests that some change in a single generation is possible.
26. There are wide variations in PTB, IUGR, LBW and their risk factors within and between countries and settings. These need to be considered in decision-making about interventions.
27. In some settings many pregnancies occur in adolescent girls who are still growing. Interventions need to consider this and their high obstetric risks.
28. IUGR and PTB are both multifactorial in etiology, and it is unlikely that interventions directed at single risk factors will have a major impact on their prevention at population level.

Summary of gaps in the evidence identified

Gap 1

Better data are required about the gestational age distribution and incidence of PTB in developing countries. This will require early identification of women who have missed their menstrual periods and/or use of early ultra sound scan dating, at least on a regional basis or in representative population-based samples.

Gap 2

Better data are required on the fetal growth (birthweight, length and head circumference for gestational age) distribution and body composition among populations living in favourable environmental circumstances in a variety of developing country settings. This will aid decisions on achievable targets for size at birth and the use of reference standards in these settings.

Gap 3

A review of the evidence is needed to understand how variations in fetal growth and gestational duration affect fetal, infant, child, and adult health outcomes, and whether the magnitude of those effects differs in different settings. This should include assessment of the role of the determinants of birthweight, particularly maternal size.

Gap 4

Examination of the temporal trends in fetal growth and gestational duration in countries that have undergone rapid economic change recently (eg Thailand, Japan, former Soviet Union countries) might aid estimation of the potential gains (and losses) in birthweight and gestation that are achievable. Similar examination could be undertaken in relation to trends in upstream factors such as maternal education and income.

Gap 5

More information is needed on the effects of potential risk factors for IUGR and PTB which have high prevalences in some developing countries. These include congenital syphilis and rubella, indoor smoke exposure, heavy maternal work, maternal anaemia and iron deficiency, and maternal diseases such as HIV/AIDS, sickle cell disease and non-malarial parasitic diseases.

Gap 6

Previous research and interventions have focused too narrowly on “downstream” individual level risk factors and too little on “upstream” societal factors, such as poverty and female education, that impact on individual women. This imbalance may explain the disparity between the relatively modest benefits of specific clinical interventions and the large population or sub-group differences between and within countries, and over time. The effectiveness of both upstream and downstream interventions should be reviewed, including consideration of universal versus targeted approaches.

Gap 7

The impact of currently on-going large-scale public health nutrition programmes should be evaluated.

Gap 8

The evidence on benefits and risks of fetal growth monitoring, including different methods of monitoring, should be reviewed.

Gap 9

Evidence on long-term consequences of micronutrient supplementation on the offspring need to be collected.

Gap 10

Reliable, population based data on major pregnancy outcomes are required in developing country settings, at least on a regional, random, sentinel or periodic basis. These data are essential to underpin management and development of maternal and child health services and programmes at clinical and public health policy levels. The collection and use of such data should be investigated.

3. SCOPE OF THE REPORT

This report describes the meeting of an advisory group of experts (listed in annex 1) which took place in Geneva in December 2002. The purpose of the meeting was to inform the development of a WHO strategy for prevention of low birthweight (LBW). The strategy will be developed following an expert consultation on LBW which will take place in November 2003.

The report gives an account of the proceedings of the meeting. It attempts to draw together consensus issues relating to the evidence on low birthweight and gaps in the evidence that were identified. Not all relevant evidence was presented at the meeting and there was discussion and debate on many of the issues. However, there was general agreement about the issues that needed to be addressed in informing the next phase of strategy development. A series of recommendations for addressing gaps in the evidence were made and are included within this report.

4. OBJECTIVES OF THE MEETING

The objectives of the meeting were:

- To review the burden of LBW
- To review the evidence for effective interventions to prevent LBW
- To identify priorities for action and make recommendations for work that needs to be undertaken to inform the expert consultation on low birthweight.

5. TERMS OF REFERENCE

1. The group will act as a source of scientific advice to assist WHO and its partners in developing a strategy to improve fetal growth and/or prevent low birthweight.
2. The group will identify scientific questions which need to be answered to inform the strategy, and advise on the state of the evidence base which addresses those questions, specifically, what is known already (and how that knowledge has been collated), what is not known, and how gaps in knowledge might be addressed.
3. The group will advise on priorities for action to improve fetal growth and/or prevent LBW.
4. The group will receive and review a draft report of the meeting.

The proposed terms of reference for the meeting were agreed.

6. FORMAT OF THIS REPORT

The format of the meeting was a series of presentations, each relating to important questions that need to be addressed in order to inform the development of a strategy to prevent low birthweight (LBW). This report summarises the main points from each presentation together with discussion points and areas of agreement.

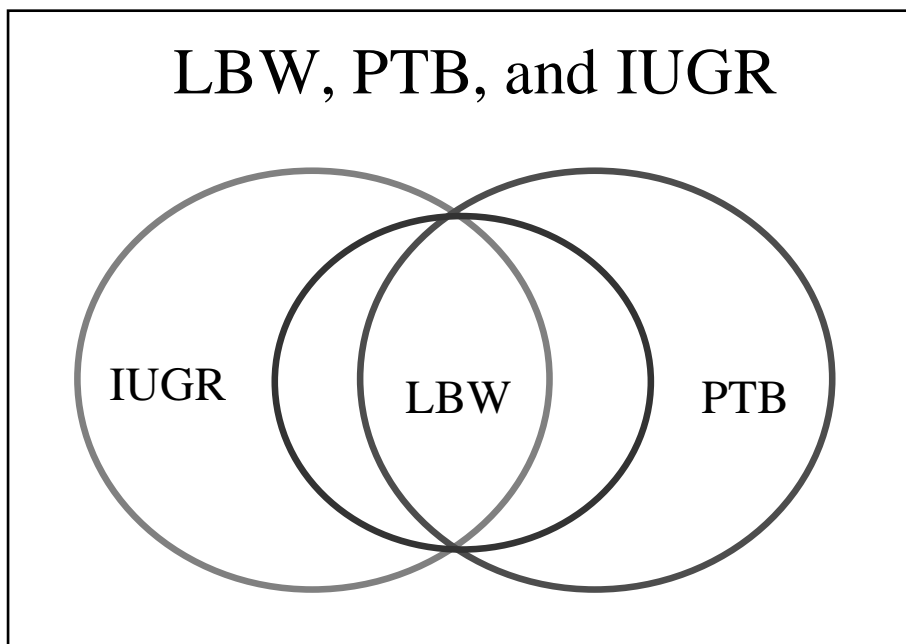
The terms ‘upstream’ and ‘downstream’ are used in the report. ‘Upstream’ refers to population-level (or distal) determinants of LBW and ‘downstream’ to individual level (or proximal) determinants.

7. INTRODUCTION

7.1 Definition of low birthweight

Low birthweight (LBW) relates to intra-uterine growth retardation (IUGR) and pre-term birth (PTB) which are two distinct processes with differing etiology and consequences. LBW is defined by WHO as a birthweight less than 2500g. IUGR has no generally accepted standard definition, but the following are commonly used: birthweight less than 10th percentile for gestational age; birthweight less than 2500g and gestational age greater than 37 weeks; and birthweight less than 2 standard deviations below the mean value for gestational age. PTB is defined as gestational age less than 37 weeks at delivery. It is important to bear in mind that only a proportion of babies with IUGR or PTB will be classified as having LBW (figure 1).

Figure 1: LBW, PTB and IUGR



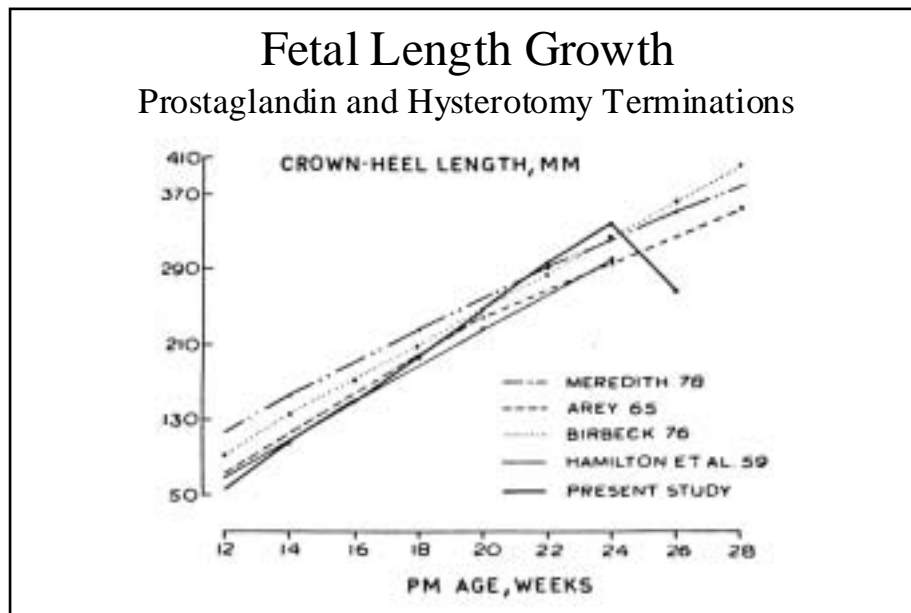
7.2 Subtypes of IUGR

Subtypes of IUGR are described according to whether restriction in growth relates more to weight or length of the fetus. Infants who are less than 10th percentile for both weight and ponderal index are classified as ‘asymmetric’ IUGR. Infants who are

less than 10th percentile for weight but not ponderal index (PI) are classified as 'symmetric' IUGR.

The existence of subtypes of IUGR has led to inferences about the timing of growth restriction, based on Tanner's schematic curves of fetal and neonatal length growth which suggested that the velocity of growth in length was greater during early pregnancy. This had led to the view that symmetric IUGR is related to earlier and more persistent impairment of growth. However real data on fetal length growth (figure 2) suggest that growth in length during pregnancy is linear. A more accurate interpretation of the different subtypes of IUGR may therefore be that 'asymmetric' IUGR reflects more severe degrees of growth restriction.

Figure 2: Crown-heel length (mm) by gestational age (PM): Comparison of series



7.3 Long-term sequelae of PTB and IUGR

PTB and IUGR are associated with early mortality and morbidity and with adverse long-term outcomes.

The long-term sequelae of PTB include:

Neurological complications such as periventricular leucomalacia, Cerebral Palsy, Seizures, delayed development, and learning difficulties.

Pulmonary outcomes such as bronchopulmonary dysplasia, recurrent wheezing with respiratory infection.

Ophthalmologic complications such as retinopathy and blindness.

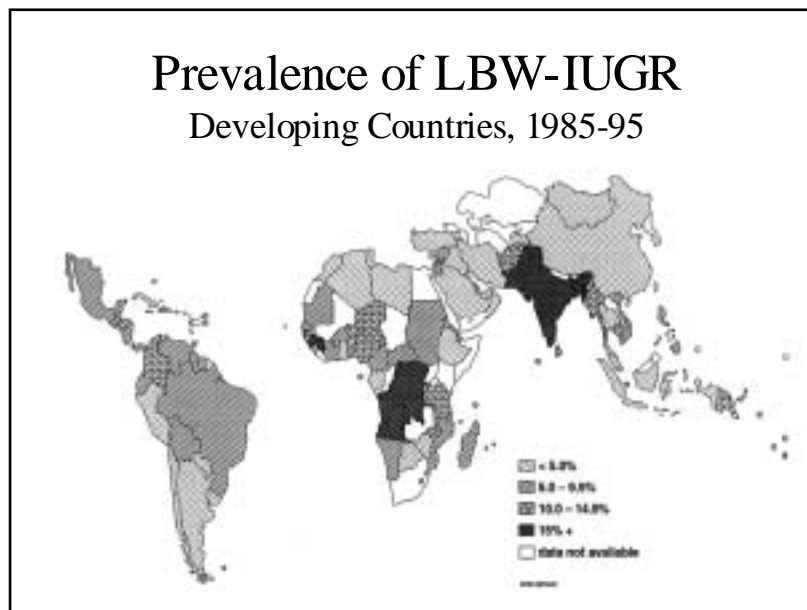
The long-term sequelae of IUGR include small permanent deficits in weight and length, mild neurocognitive deficits and increased risk of hypertension, coronary heart disease and diabetes in adult life.

7.4 Prevalence of LBW-IUGR

The highest rates of IUGR are seen in the Indian subcontinent and South Africa (figure 3). Moderately high rates of IUGR are seen in parts of Latin America and in

other parts of Africa. There are, however, areas of the less developed world where prevalence is low, such as China and Chile.

Figure 3: Prevalence of LBW-IUGR in Developing Countries

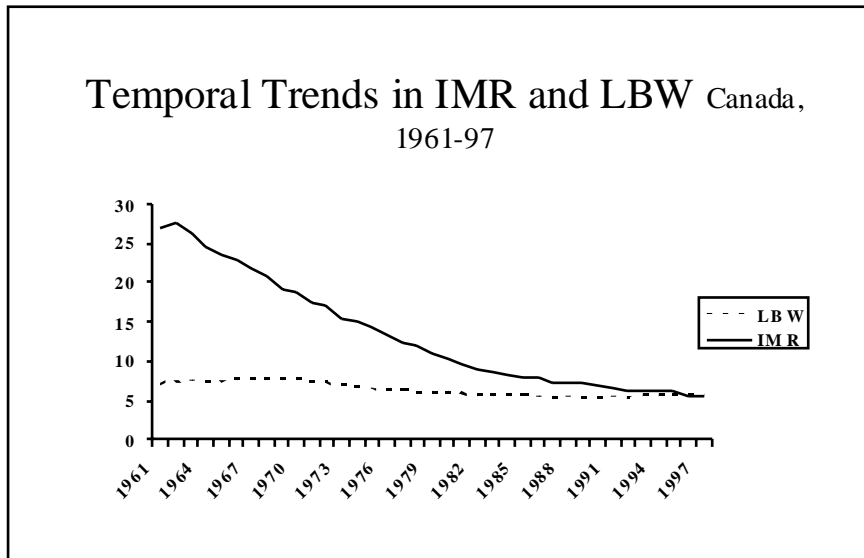


7.5 Trends in PTB and LBW in developed countries

Data from Canada relating to temporal trends in LBW and PTB were presented. These showed that in recent years there has been a marked increase in PTB in developed countries. Despite this there has not been an decrease in mean birthweight. These trends can be explained by the fact that there has been an increase in the mean birthweight of term babies at the same time as the preterm birth rate has increased and the rate of post-term births and stillbirths has decreased. The factors underlying these trends are thought to be improvements in obstetric care and increased obstetric interventions during pregnancy, and increased fertility treatment which has led to increasing multiple births. Together these factors are thought to account for the increase in PTB. Trends for increase in mean birthweight and birthweight for gestational age are related to increases in maternal pre-pregnancy BMI and gestational weight gain and reduction in maternal smoking.

Temporal trends in Infant Mortality Rate (IMR) and LBW in Canada from 1961 to 1997 show a dramatic decline in IMR over this time despite little change in the rate of LBW (figure 4). Similar trends have been observed in other developed countries and some parts of the developing world such as Brazil. However little data is available for the majority of developing countries. These trends suggest that reducing infant mortality does not require the prevention of LBW.

Figure 4: Temporal trends in IMR and LBW in Canada 1961-97



7.6 Discussion points:

Although it is clear that a great deal is known about the burden of LBW and temporal trends in LBW in developed countries, there is little comparable data available from developing countries.

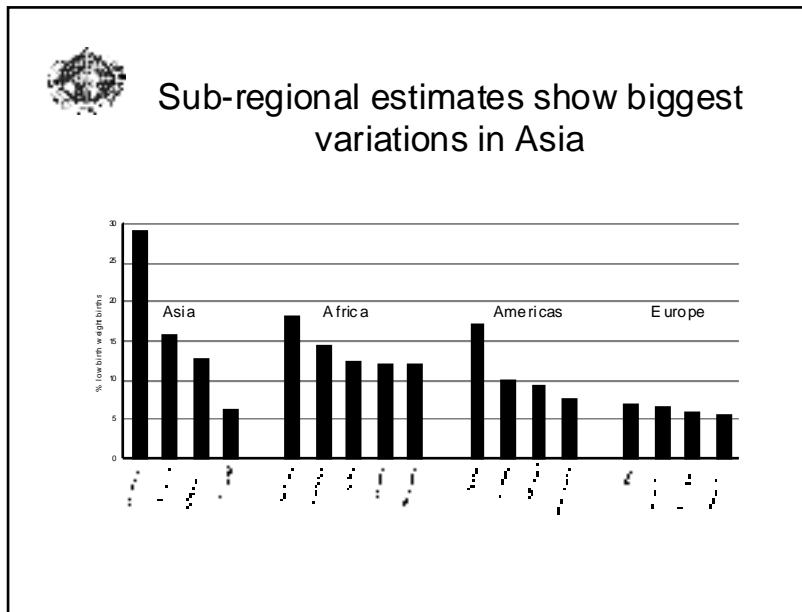
There are many outcomes that should be considered in addition to infant mortality. As demonstrated by the range of long-term sequelae of PTB and IUGR it is important to consider morbidity, quality of life and developmental status. It was also agreed that the outcomes considered should not just be early outcomes but should relate to later stages in the life course.

8. WHO GLOBAL AND REGIONAL ESTIMATES ON LOW BIRTHWEIGHT

WHO global and regional estimates on LBW were presented. These data are based on a number of sources including birth registries, surveys, special studies and hospital data. Estimates based on these sources show that the proportion of infants born less than 2500g is decreasing slowly. However, it is far from clear that these estimates represent an accurate picture for many developing countries where there is poor access to birthweight data. The proportion of infants who are weighed at birth is very low in many developing countries where only a small proportion of births occur in hospital. For example in the period from 1995 to 2000 the proportion of babies weighed at birth in Asia and Africa were 27% and 26% respectively.

WHO sub-regional estimates of LBW rates were presented. This data showed the wide diversity of rates within developing regions such as Africa and Asia (figure 5).

Figure 5: Sub-regional LBW rate estimates



Point of agreement:

It was agreed that progress needs to be made in collection of routine birthweight data in developing countries, that is comparable with that collected in other countries and is standardised.

9. WHAT IS THE NATURE OF THE EVIDENCE AND HOW CAN WE USE IT?

9.1 Breadth of the enquiry

It was agreed that the scope of the WHO strategy to prevent LBW should be broad, considering a wide range of determinants of LBW and not focussing solely on maternal nutrition.

9.2 Types of evidence and methodological issues

It was acknowledged that much of the evidence that would be considered when exploring the determinants of LBW would be observational, however it was agreed that where the evidence was robust and biologically plausible it was not always necessary to have evidence from randomised controlled trials (RCTs) to infer causation. It was suggested that RCT evidence should be available for research on interventions and the group agreed that this was important when measuring intended benefits of interventions. However, it was acknowledged that RCTs may not be feasible for some important types of intervention, for example fiscal policy, which might have important contributions to make in the prevention of LBW.

9.3 Gaps in the evidence

One of the major gaps in the evidence is the lack of comprehensive data relating to the extent of the problem of LBW and the burden of disease resulting from it, particularly in developing countries. Other gaps are formal systematic reviews in some areas (Cochrane reviews and some aetiological reviews are exceptions), experimental

evidence at community/country level, evidence on attributable risk and evidence on cost-effectiveness of interventions. The range of outcomes studied is often limited; for example adult cardiovascular disease has been studied extensively in relation to birthweight but the evidence relating to cancers has not often been considered. This is of importance since the association of birthweight and cancer may run in a different direction to that of cardiovascular disease.

It was acknowledged that many of the gaps in the evidence may relate to non-researchable but important questions since researchers are likely to have chosen to research areas where research can be carried out.

9.4 Framework for the development of the strategy (annex 3)

There was general agreement that the proposed framework for knowledge gathering and analysis to inform the development of the strategy provided a useful basis for the work of this meeting. The framework outlines a series of questions that need to be addressed in the development of a strategy and the emphasis is on a broad range of determinants of fetal growth/LBW and also a broad range of outcomes of LBW. In accordance with this framework, it was agreed that the recommendations generated as a result of this meeting should be comprehensive in addressing both determinants and outcomes of LBW.

10. WHAT ARE WE TRYING TO ACHIEVE - PREVENTION OF LOW BIRTHWEIGHT OR WIDER IMPROVEMENT IN FETAL GROWTH?

10.1 What outcomes are important?

The importance of considering a broader range of outcomes than just mortality, including morbidity, longevity, quality of life (health and non-health related), developmental status and health-related behaviour was discussed. It was agreed that these outcomes should be considered not only in relation to infancy but across the life course (i.e. childhood, adolescence and adulthood). The balance of early and late effects and of beneficial and non-beneficial effects was seen as another important issue for consideration. For instance, increased size at birth might have beneficial effects in terms of reduction in infant mortality, but might lead to increased risk of disease in adult life such as cancer. The values people place on early and later outcomes will therefore be important factors to consider.

It was agreed that the role of maternal size in determining LBW needs to be considered and that the lack of knowledge in this area represents a significant gap in the evidence. There is an inherent balance between the mother and baby, and maternal size is a constraining factor on the growth of the fetus during pregnancy. It is difficult to assess the risk of adverse outcomes associated with LBW without first considering maternal size, since LBW infants of small mothers who have had their growth appropriately constrained may well have lower risks of adverse outcomes associated with their birthweight than other LBW infants.

10.2 What is optimal growth?

There is little evidence for thresholds at top or bottom of the birthweight distribution. The relationship between birthweight and early and later outcomes appears to be continuous, as shown by evidence relating to adult chronic disease and early outcomes such as SIDS. However, it was agreed that in order to facilitate monitoring of trends in low birthweight, it is important that the thresholds from the past continue to be measured.

The birthweight distribution differs according to setting. There are differences both within and between countries. This has a bearing on the potential risks and benefits of shifting the birthweight distribution and it was agreed that it is important to consider how to intervene in any given setting in order to avoid harm. There are particular issues for developing countries partly because of small maternal size. For example, in Bangladesh women are small and it is therefore feasible that harm may be caused, in terms of increase in maternal and perinatal mortality and morbidity, if the birthweight distribution is shifted too far to the right. In India, it has been suggested that there is a potential danger that supplementation during pregnancy could lead to fatter babies, rather than uniform increase in growth and it is unclear what the long-term sequelae of this would be.

Research evidence suggests that the consequences of shifting the birthweight distribution may be difficult to predict. A study reporting data on optimal birthweight in different European countries demonstrated that for every 100g increase in modal birthweight, the optimal birthweight rose by 170g¹. In other words, the higher the average birthweight the further the the mean is from the optimum. The reasons for this paradox are not well understood but it is important for the purposes of developing a LBW strategy to acknowledge that such a paradox exists.

10.3 Measurement of fetal growth

There was discussion of how fetal growth should be measured and it was acknowledged that collection of data on fetal growth (birthweight, length, head circumference for gestational age) and body composition is poor, particularly in developing countries. It was suggested that, since there is an inherent balance between mother and baby, an approach to assessing fetal growth could be to aim to detect when this balance has been disturbed by assessing catch-up and catch-down growth post-natally. However concerns were expressed about how useful this approach would be in developing countries since patterns of growth after birth will depend on environmental conditions which are unlikely to be optimal in developing countries.

10.4 Gestational age

It was agreed that the paucity of information relating to gestational age in developing countries is a contributory factor to the major gap in the evidence relating to the determinants of PTB and its impact on early and later outcomes.

10.5 Points of agreement

There is a gap in the evidence in terms of what birthweight and post-natal growth are optimal for a range of outcomes.

The birthweight distribution needs to be linked to a range of outcomes before conclusions can be made about appropriate thresholds or shapes of distribution.

11. WHAT DETERMINES OPTIMAL FETAL GROWTH/LOW BIRTHWEIGHT?

11.1 Determinants of IUGR and PTB

Etiologic fractions (EF) were reported for determinants of IUGR and PTB in developed and developing countries. The EF is the proportion of the outcome in a given population that can be attributed to a given risk factor, and is therefore determined both by the relative risk of the outcome and prevalence of the risk factor in the population.

In developed countries the major determinants of IUGR include cigarette smoking, low weight gain, low BMI, primiparity and short stature (see figure 6). In developing countries the major attributable causes of IUGR include low weight gain, low BMI, short stature, malaria and pregnancy-induced hypertension although a substantial component is due to unknown causes (see figure 7).

Figure 6: Attributable causes of IUGR in developed countries

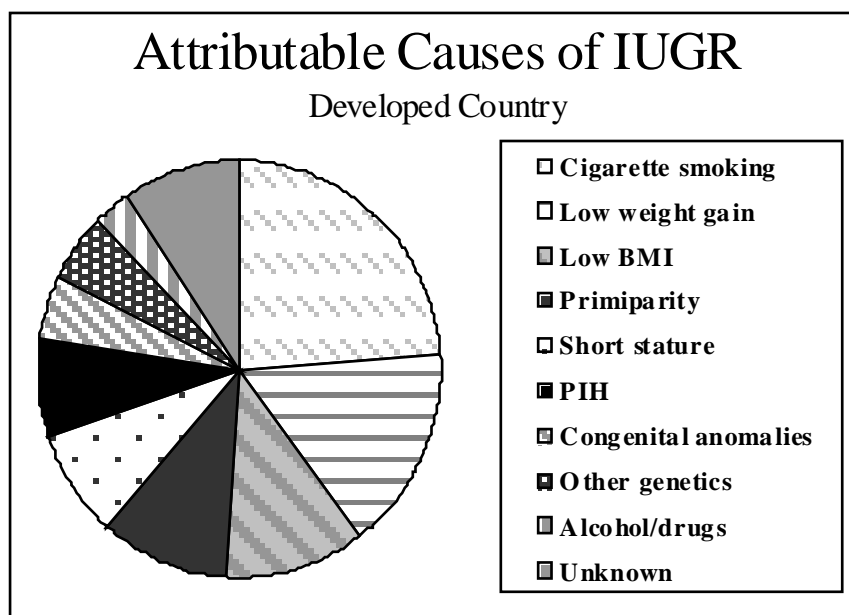
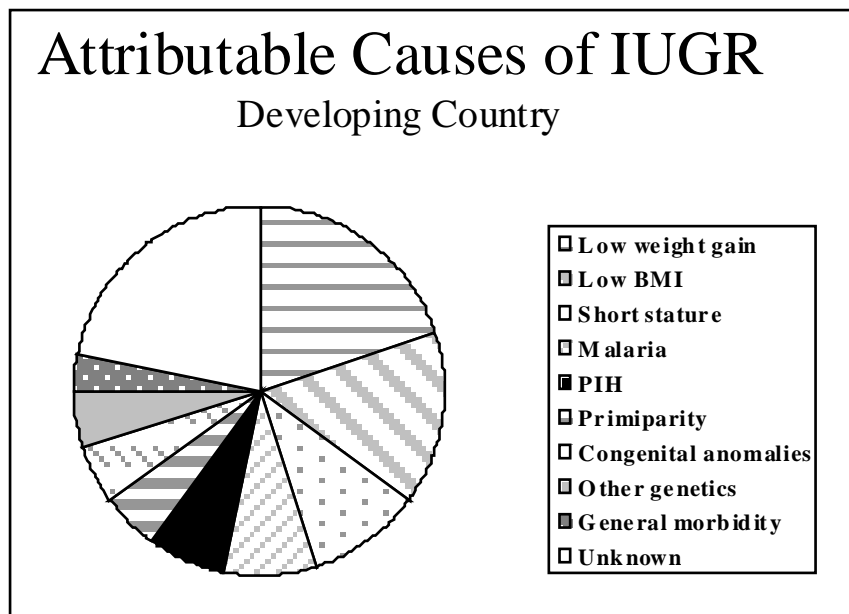


Figure 7: Attributable causes of IUGR in developing countries



Much less is known about the determinants of PTB. In developed countries the major attributable causes of PTB were ‘unknown factors’, genito-urinary infection, multiple births and pregnancy-induced hypertension. There is insufficient data from developing countries to give any clear picture of causes of PTB particularly since gestational age is so poorly recorded.

Evidence from the WHO collaborative study on maternal anthropometry and pregnancy outcome was presented (figures 8 and 9)². This shows that maternal anthropometry (short stature, low BMI and low weight gain) in pregnancy is more strongly associated with risk of IUGR than with PTB suggesting that macro-nutritional effects on gestation are small compared with their effects on fetal growth.

Figure 8: Maternal anthropometry and odds ratio of IUGR

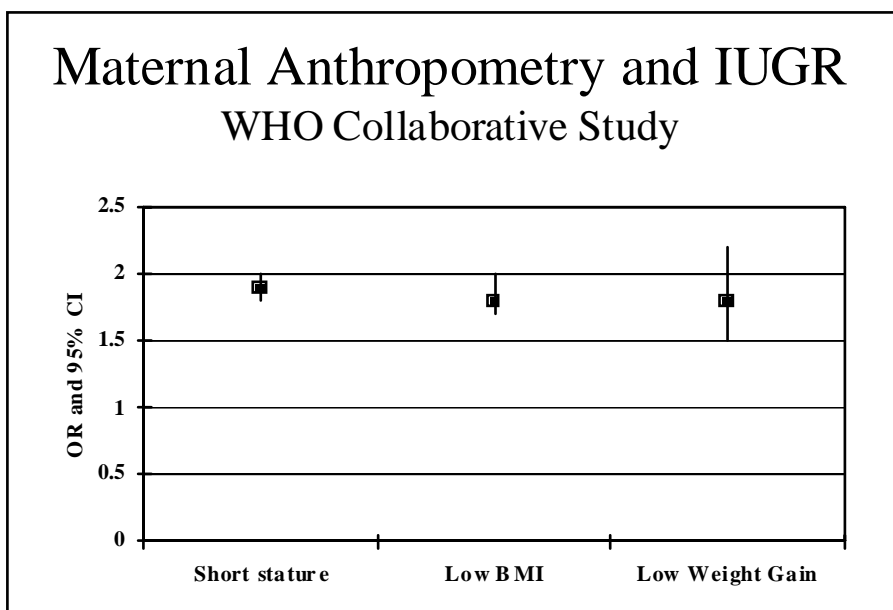
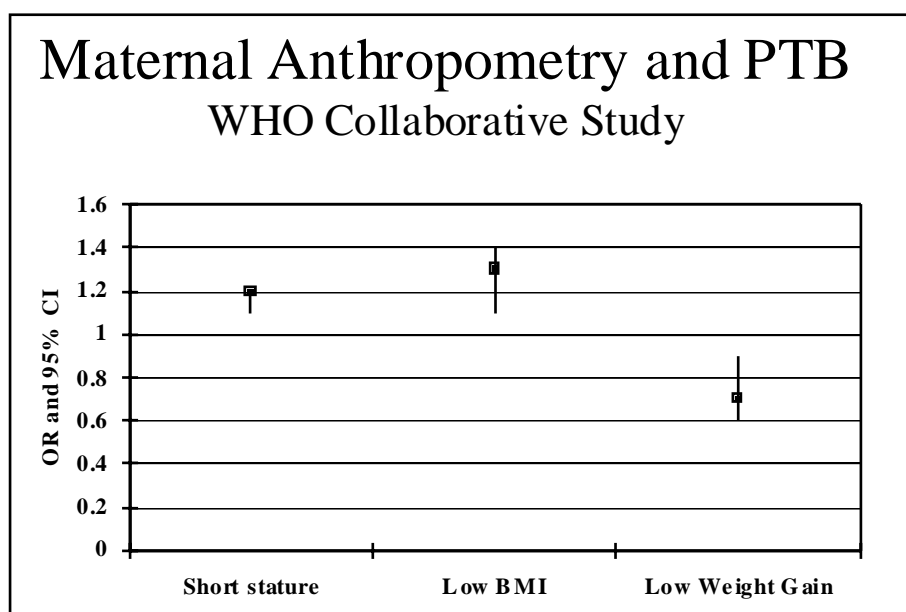


Figure 9: Maternal anthropometry and odds ratio of PTB



11.2 Prevention of PTB and IUGR

Evidence from RCTs on interventions to prevent low birthweight was summarised. Interventions that have been shown to be effective in preventing PTB include:

- Counselling to reduce cigarette smoking
- Treatment of asymptomatic bacteruria
- Fish oil supplementation
- Cerclage in women with cervical incompetence

Interventions that have been shown to be effective in preventing IUGR include:

- Food supplementation (at a macro-nutrient level)
- Counselling to reduce cigarette smoking
- Malarial prophylaxis in primiparous women
- Low-dose aspirin in women at high risk

It was acknowledged, however, that the majority of this evidence comes from RCTs in developed countries and there is little evidence from developing countries.

11.3 Discussion points:

11.3.1 The evidence presented had focused on individual-level (downstream) determinants of low birthweight. It was pointed out that it is important to gain an understanding of the influence of upstream (population-level) factors such as poverty and maternal education. However the lack of evidence in these areas means that it is difficult to assign attributable risk to such upstream factors.

11.3.2 The evidence on individual level factors suggests that high rates of IUGR in developed countries are linked to poverty because of associations with shorter stature, smoking and low weight gain. More research is needed into the interventions which

are differentially effective at targeting the effects of poverty. Research to date has failed to show any effect on LBW but this may have been due to difficulties in designing studies to test this question. For example, in a trial of psycho-social support to prevent LBW during high risk pregnancies, the intervention was unable to change the levels of stress or anxiety and therefore could not be expected to change the final outcome – LBW³.

11.3.3 The influence of smoking on LBW in developing countries may increase due to increasing prevalence of smoking in young women.

11.3.4 A number of other determinants of low birthweight were discussed:

It was agreed that at present there was insufficient evidence to support the use of micronutrients, such as iron and zinc in prevention of PTB and IUGR.

Maternal obesity is a major cause of stillbirth and increased caesarean section rate and it is important to bear in mind that the impact of obesity on pregnancy outcome is likely to become increasingly relevant because of the increasing prevalence of obesity in developed and some developing countries.

11.3.5 Concern was expressed that more attention needs to be paid to the length of gestation as an issue and that it is difficult to think about addressing the determinants of PTB when there is often no information on the last menstrual period of a woman coupled with a poor standard of obstetric care as is often the case in developing countries. The problem is compounded by health providers failing to record information on gestation even when it was available.

11.3.6 One of the gaps in knowledge relates to timing of interventions to prevent LBW. It is not clear when it is best to intervene. There was general agreement that it makes sense to intervene pre-pregnancy to improve the health and nutritional status of women in order to reduce their risk factors for LBW, but there is little evidence to inform this.

11.4 Points of agreement:

- That it was important to consider both upstream and downstream factors as determinants of IUGR and PTB.
- That there are gaps in the evidence relating to the impact of upstream factors and interventions to address them.
- That evidence relating to determinants of PTB is poor and this is in part due to poor recording of gestational age in developing and some developed countries.
- That there are gaps in the evidence about when to time interventions aimed at preventing LBW, although knowledge of the determinants suggest that it is most appropriate to intervene before pregnancy.

12. WHAT INTERVENTIONS MIGHT BE EMPLOYED TO PROMOTE FETAL GROWTH/PREVENT LOW BIRTHWEIGHT?

12.1 Interventions to prevent PTB

The available evidence on prevention of PTB is limited and much more work needs to be done. There is some evidence from RCTs to suggest that reduction in smoking, treatment of bacteruria, use of fish oil supplements and cerclage in women with cervical incompetence are effective in reducing PTB.

It was suggested that reduction in workload was an additional candidate because of observational evidence from developing countries. Evidence from the Gambia was presented to support this point⁴. A marked reduction in mean birthweight is observed during the summer months, which is a direct consequence of reduction in gestational age (Figure 10). This time of year, which is referred to as the hungry season, corresponds to a time when women have to undertake intensive farm labour. The reduction in mean birthweight and gestational age are paralleled by a sharp increase in PTB and LBW at this time of year (Figure 11).

Figure 10: Seasonal variation in mean birthweight and gestational age

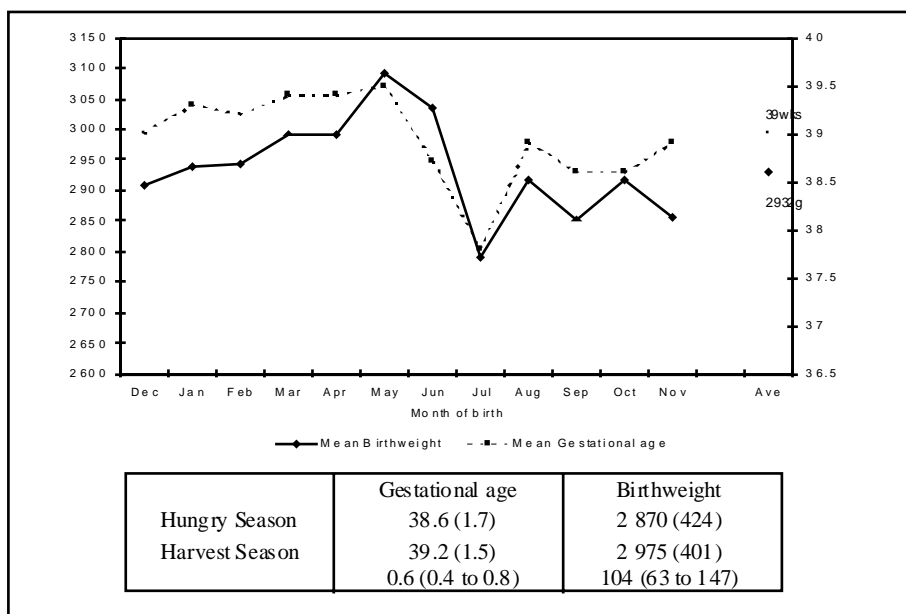
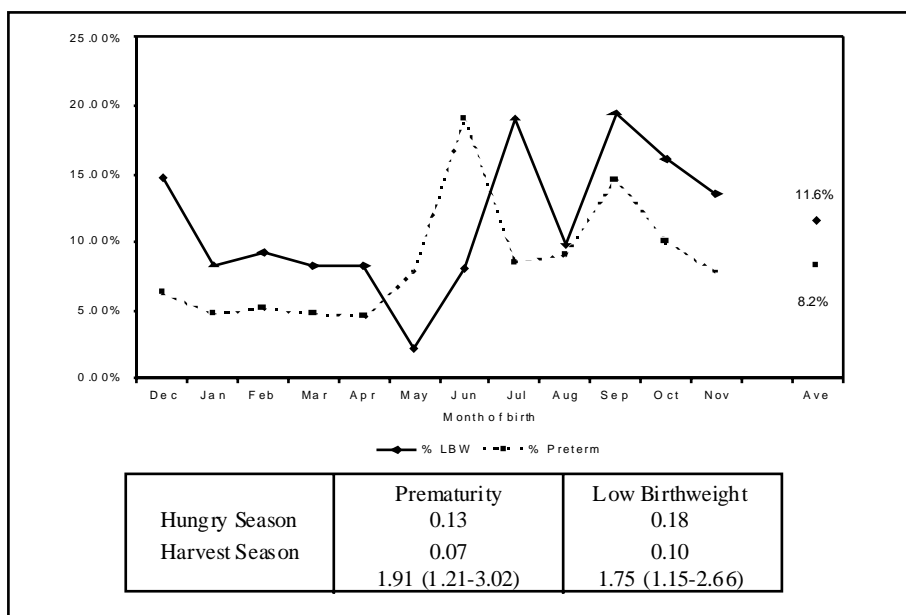


Figure 11: Seasonal variation in rates of PTB and LBW



12.2 Interventions to prevent IUGR

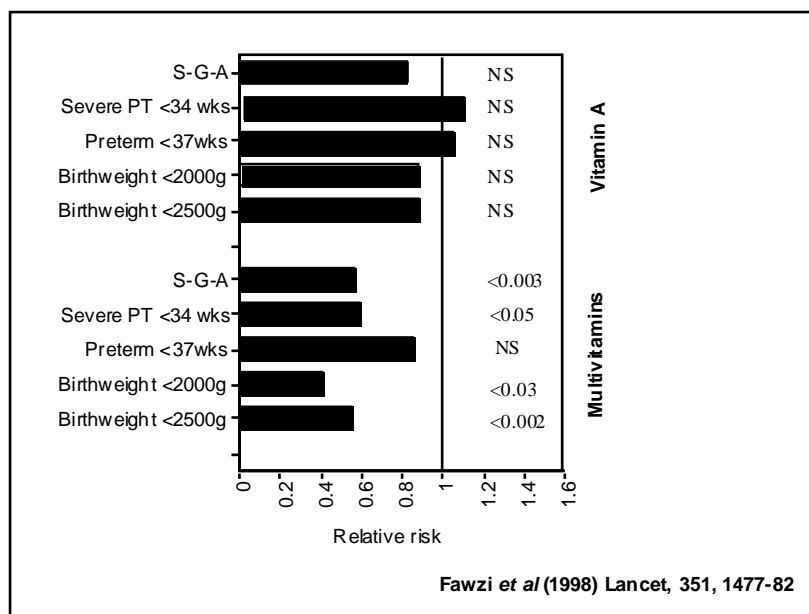
12.2.1 More is known about prevention of IUGR. However the multifactorial nature of the problem makes it difficult to prevent through one single intervention. Fetal growth is regulated by endocrine processes and when considering what interventions might work it is important to consider how to influence these processes, some of which will be genetically determined.

12.2.2 Although some of the determinants of IUGR are non-modifiable, such as altitude and genes, there are many potentially modifiable factors. Modifiable factors occurring pre-pregnancy are maternal stature, BMI, age and birth interval. Factors occurring during pregnancy are maternal weight gain, micronutrient status, energy and protein intake malaria, smoking/pollution, violence and stress.

12.2.3 Evidence on dietary supplementation

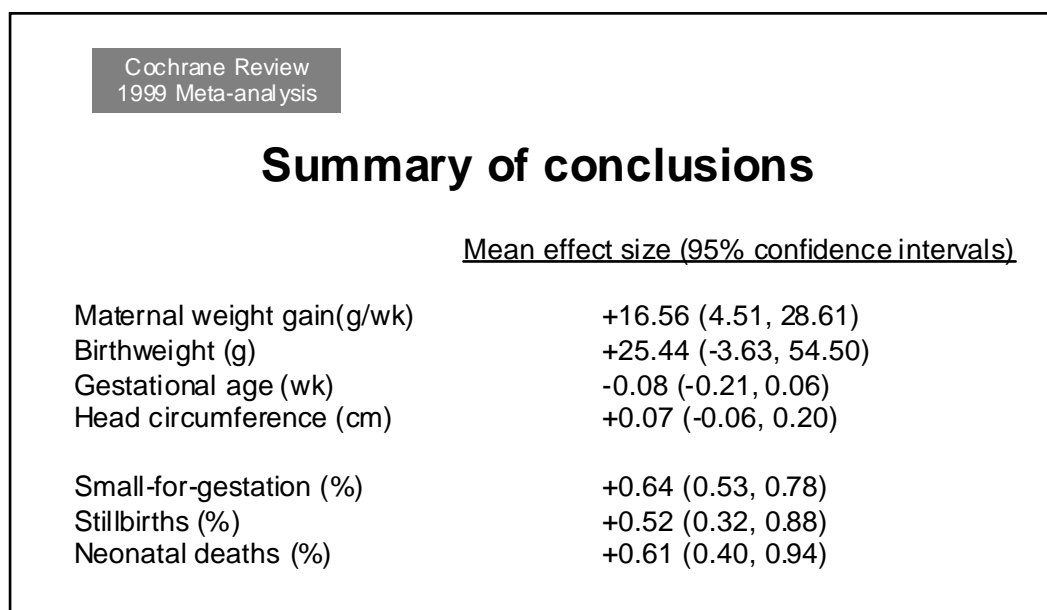
Evidence from trials of dietary supplementation during pregnancy was presented. Trials of protein/energy supplementation during pregnancy in rural Gambia showed significant reduction in LBW and stillbirth in the supplementation group. These effects were particularly pronounced in the hungry season. Trials by Fawzi et al of multivitamin supplementation during pregnancy showed significant reduction in preterm births, stillbirths and miscarriage rates (figure 12)⁵.

Figure 12: Effects of pre-term delivery and size at birth



A Cochrane systematic review of the evidence on protein/energy supplementation was carried out in 1999⁶. The findings of a meta-analysis revealed small effects on maternal weight gain and birthweight as well as modest reductions in rates of small-for-gestational-age, stillbirths and neonatal deaths (figure 13). However, there was no evidence that supplementation was associated with long-term benefit for the offspring or beneficial effects on maternal health.

Figure 13: Cochrane systematic review on balanced protein/energy supplementation in pregnancy: results of meta-analysis



12.3 Other important issues when considering interventions to reduce LBW include:

- There is uncertainty, due to lack of evidence, as to the appropriate timing of interventions to prevent LBW. It is also unclear how much can be achieved in a single generation because of the inter-generational cycle of IUGR.
- More weight should be given to the practicality and cost-effectiveness of interventions. For example the ongoing trial of supplementation in Bangladesh is very labour-intensive and brings sustainability into question.
- Due to the multi-factorial nature of IUGR the point was made that upstream interventions, such as wealth creation or maternal education, have a major advantage over downstream interventions in that they influence many factors at once.

12.4 Discussion points:

12.4.1 There was agreement that interventions that target upstream issues may be effective and that the emphasis for intervention should be put on influencing the determinants of LBW in a holistic way. The example was given of a recent non-randomised trial of neonatal care provided by healthworkers in rural areas of India who were trained to recognise and treat infection in newborn infants⁷. This intervention led to a significant reduction in neonatal mortality. Although this study related to neonatal mortality rather than LBW, it demonstrates the point that interventions that target upstream issues can be effective.

12.4.2 The Dutch famine studies were discussed in terms of what could be learnt from them about timing of malnutrition and inter-generational effects. The studies showed that there were profound effects (up to 300g differences in birthweight) on fetal growth due to undernutrition in the third trimester. However, the evidence on inter-generational effects is inconsistent. The point was also made that the generalisability of the findings of these studies may be limited in that women who did conceive during the famine may be different from those who did not, genetically or metabolically.

12.4.3 The role of preconceptual nutritional interventions was discussed. Evidence to date does not support the use of these although intuitively they make sense. A trial of supplementation in Taiwan had targeted women after delivery to ensure that they had received supplementation before their next pregnancy. However the effect on LBW was similar to that seen in a group who only received supplementation during pregnancy.

12.4.4 Variations in birthweight distribution and shape and size of baby will have a bearing on the effectiveness of interventions. There is insufficient knowledge of what is 'normal' in developing countries such as India to allow appropriate intervention to shift the birthweight distribution.

12.5 Points of agreement

There are gaps in the evidence on effectiveness of upstream and downstream interventions and the appropriate timing of interventions. More information is needed on the practicality and cost-effectiveness of large-scale interventions.

13. HOW DO ISSUES VARY BETWEEN DIFFERENT SETTINGS AND POPULATIONS?

13.1 Determinants of variations in birthweight

Recent evidence summarising the contribution of genetic and environmental factors to the variation in birthweight was presented (figure 14)⁸.

Figure 14: Genetic and environmental contributions (%) to birthweight variations

Genetic and environmental contributions (%) to birthweight variation.	
Genetic	
Maternal genotype	20
Fetal genotype	16
Fetal sex	2
Total genetic contribution	38
Environmental	
General maternal environment	18
Immediate maternal environment	6
Maternal age and parity	8
Unknown environmental influences	30
Total environmental contribution	62

Stephenson T, Symonds ME. Arch Dis Child 2002;86:F4-F6.

Around 60% of the variation in birthweight can be attributed to environmental factors. However, unknown environmental influences account for around 50% of the variation attributed to these factors. It was acknowledged that there are likely to be wide variations in the relative contribution of these factors in different settings.

13.2 Maternal anthropometry

The wide variations in maternal anthropometric measurements according to setting were demonstrated using data from the WHO collaborative study on maternal anthropometry and pregnancy outcomes (figure 15)². For example the height of women in Guatemala was 148 cm compared with 163 cm among white American women. The pre-pregnancy BMI of women in Pune, India was 18.3 kg/m² compared with 22.2 kg/m² in women in the UK and 23.72 kg/m² in white American women. These measurements correspond to the 50th percentile. Likewise wide variations in weight gain during pregnancy were observed. For example in Malawi the weight gain was 4.7 kg compared with 14.4 kg in white American women and 11.6 kg in the UK. Data on weight gain during pregnancy was not available for a number of the least developed countries participating in the study such as India and rural Nepal where the weight gain is likely to have been even lower.

Figure 15: Maternal anthropometric measurements among countries participating in WHO collaborative study

Country	Height (cm)	Prepregnancy BMI*	Weight gain (kg)
Argentina	157	22.4	10.8
Myanmar	151	19.8	-
China	160	19.5	11.7
Colombia	155	23.3	10.1
Cuba	157	21.8	4.6
Gambia	157	19.7	6.5
Guatemala	148	20.8	7.1
India (Pune)	150	18.3	-
Indonesia	149	20.2	-
Ireland	158	23.7	11.0
Malawi	155	21.0	4.7
Nepal (Rural)	150	19.5	-
Sri Lanka	150	18.8	-
Thailand	153	20.8	8.0
UK	159	22.2	11.6
US/CDC (Black)	162	23.1	13.5
US/CDC (Hispanic)	158	23.7	12.8
US/CDC (White)	163	22.6	14.4
Vietnam	152	19.6	5.6

13.3 Pregnancy outcome

Further data from the WHO collaborative study was presented to demonstrate the wide variations in pregnancy outcome according to setting (figure 16)². For example, the percentage of live births classified as having IUGR was 54.2% in Pune, India compared with 6.9% in Ireland and 12.3% in the UK. The percentage of live births that were born prematurely (defined as gestational age below 37 weeks at delivery) was 21.3% in Thailand compared with 4.6% in the UK.

Figure 16: Pregnancy outcome among countries participating in WHO collaborative study

Country	LBW (% of live births)	IUGR (% of live births)	Preterm Birth (% of live births)
Argentina	6.3	9.7	7.2
China	4.2	9.4	7.5
Colombia	16.1	17.8	15.7
Cuba	8.1	14.7	7.2
Gambia	12.1	13.5	13.5
Guatemala	12.5	25.3	15.8
India (Pune)	28.2	54.2	9.7
Indonesia	10.5	19.8	18.5
Ireland	5.6	6.9	6.2
Malawi	11.6	26.1	8.2
Myanmar	17.8	30.4	24.6
Nepal (Rural)	14.3	36.3	15.8
Sri Lanka	18.4	34.0	14.0
Thailand	9.6	17.0	21.3
United Kingdom	6.2	12.3	4.6
US/CDC (Black)	10.6	11.2	16.6
US/CDC (Hispanic)	4.8	5.8	10.2
US/CDC (White)	6.0	6.9	9.3
Vietnam	5.2	18.2	13.6

13.4 Variations in risk factors for LBW

There are likely to be wide variations in the prevalence of risk factors according to setting. This point was demonstrated in relation to cigarette smoking. World Bank data on prevalence of smoking in women aged 15 years and over according to region was presented (figure 17)⁹. This showed that the prevalence of smoking in this group ranged from 1% in South Asia to 26% in Eastern Europe and Central Asia. There are also wide variations within countries, as is true in the case of Latin America where smoking prevalence is known to be as high as 35% in some areas although the overall prevalence for the region was 21%.

Figure 17: Prevalence of smoking among women aged 15 years or older by region

Region	Prevalence (%)
East Asia and Pacific	4
Eastern Europe and Central Asia	26
Latin America and Caribbean	21
Middle East and North Africa	5
South Asia	1
Sub-Saharan Africa	10

World Bank 1999.

Data from Pelotas in Brazil was presented showing prevalence of maternal smoking of 33.5%¹⁰. Around a quarter (25.5%) of IUGR and 17.7% of PTB can be attributed to smoking in pregnancy. Further data from Pelotas showed that prevalence of smoking during pregnancy was strongly associated with maternal education (figure 18) and that more educated women were less likely to smoke and that there was a higher rate of stopping smoking during pregnancy in this group. This data was seen as highlighting the importance of smoking cessation interventions and maternal education as interventions to reduce LBW.

Figure 18: Prevalence of smoking during pregnancy according to maternal education. Pelotas, Brazil, 1993

Low birthweight, IUGR, preterm birth and maternal smoking. Pelotas, Brazil, 1993			
	Smoking prevalence	Adjusted OR	Etiologic fraction
LBW	33.5%	1.59	17.7%
IUGR	33.5%	2.07	25.5%
Preterm	33.5%	1.09	-

Horta BL et al. Paediat Perinat Epidem 1997; 11: 140-51.

13.5 Discussion points

13.5.1 The evidence on use of smoking cessation interventions in developing countries shows that they have only had a modest effect to date. However the secular trends for reduction in smoking in developed countries over the last 20 years suggest that economic improvements may lead to reduction in smoking. This suggests that upstream interventions may be more effective in reducing smoking during pregnancy. It is important to consider the socio-economic differentials in risk factors since those who are worst off may be least likely to benefit from interventions. It was agreed that the association of smoking with deprivation was an important consideration.

13.5.2 There was general agreement that it is important to address socio-economic and other differentials/inequalities within populations. In order to do this it will be important to obtain better data on fetal growth distribution among populations living in favourable environmental circumstances in developing countries to find out what targets for size at birth are achievable.

13.5.3 There was discussion of other risk factors for low birthweight:

- Alcohol consumption is linked to low birthweight and can cause Fetal Alcohol Syndrome. There is no clear threshold at which harm occurs, although equally there is no evidence that intake up to 2 units each day is associated with LBW or effects on fetal growth.
- The impact of misuse of substances other than cigarettes should also be considered such as chewing tobacco.
- The evidence for the impact of infection on low birthweight should be considered, and although malaria and diarrhoeal diseases had been discussed, it was agreed that the evidence relating to syphilis, HIV and rubella should also be considered.
- Environmental determinants of low birthweight were discussed. There is relatively little evidence relating to the impact of environmental factors on low birthweight but what there is suggests that noise, air pollution and chlorination of

water have a small effect in increasing the risk of adverse pregnancy outcome. Studies of indoor household smoke have shown that women living in these sorts of environment have comparable levels of carbon monoxide in their bloodstreams to women who smoke. It was agreed that it was important to consider these along with other determinants of low birthweight.

- Other maternal diseases such as sickle cell disease and iron deficiency anaemia were also flagged up as potentially important determinants of low birthweight.

13.6 Points of agreement:

- The variation between different countries and populations will influence priorities for intervention.
- The developed and developing countries dichotomy is a gross oversimplification since there will be wide variations and inequalities within countries. Gaps in knowledge about variations in fetal growth/LBW within and between countries need to be addressed to inform the development of a strategy.

14. WHAT ARE THE POSSIBLE TIMESCALES FOR ACTION?

14.1 Evidence from developing countries

In developing countries such as India and Bangladesh, a very high proportion of births occur to teenagers who are still growing themselves and are at greater obstetric risk than other women. For example, there were 115 births per 1000 in girls aged 15-19 years in Bangladesh and 109 per 1000 in India compared with 5 per 1000 in China. Data from Uttar Pradesh in India reveals that 40% of girls marry before adolescence and a high proportion of these are malnourished (BMI <18.5). The average weight gain in pregnancy for these women is around 5kg. They also have a higher risk of obstetric complications due to higher risk of obstructed labour.

Data from rural Kerala demonstrated that girls aged 15 and under were at greater obstetric risk by virtue of their lower weight and height than women aged 18 years (figure 19).

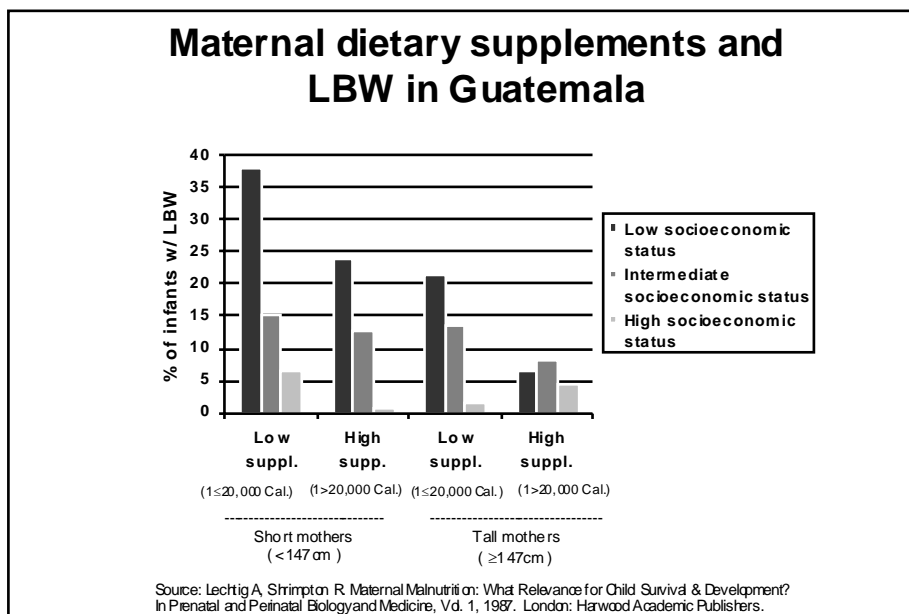
Figure 19: Percentage of women in rural areas at obstetric risk at different ages in Kerala

<i>Teenage Pregnancy</i>		
• Percentage of rural “women” at obstetric risk at different ages in Kerala		
Age (yrs)	% <38 kg	% <145 cm
14	68	45
15	47	29
18	24	16

Source: Gopalan 1987

Data from an intervention study of maternal dietary supplementation during pregnancy in Guatemala showed that interventions may have differing effects according to socio-economic status and maternal anthropometric measurements (figure 20)¹¹. The greatest reduction in LBW as a result of the intervention was seen in the tall women of low socio-economic status. However, it is important to note the strong influence of socio-economic status on background levels of LBW: rates of LBW were normal (<5%) in the women of high socio-economic status even amongst those of short stature who were assigned to the low supplementation group.

Figure 20: The effect of maternal dietary supplementation on LBW in Guatemala according to socio-economic status and maternal stature



14.2 Inter-generational effects

Migrant studies provide important information about inter-generational effects and suggest that interventions may be effective in preventing LBW within a single generation. Evidence based on studies of migrants to the United States and Norway was presented. Rates of LBW fell from 15.9% to 8.5% in Asian immigrants to the USA over the 10-year period from 1978 to 1989¹². Similarly, migrants to Norway from Vietnam, Pakistan and North Africa showed similar rates of LBW to those prevailing in Norwegians¹³. However a recent study of Indian migrants to Southampton (UK) failed to show a change in birthweight over 40 years¹⁴.

14.3 Should interventions be targeted during pregnancy?

The argument was put forward that poor pre-natal growth programmes poor post-natal growth and therefore it is important to target interventions during pregnancy. The findings of an ecological study exploring the determinants of childhood underweight and stunting using country level data were presented¹⁵. This study revealed that childhood underweight was significantly associated with LBW, anaemia in pregnancy and intake of animal protein during pregnancy (figure 21).

However these findings do not necessarily indicate that pre-natal growth predicts post-natal growth since the associations will be confounded by socio-economic status

which will have a strong influence on childhood growth as well as predicting poor diet and anaemia during pregnancy. It was also agreed that pre-natal growth is unlikely to programme post-natal growth since following birth, once maternal constraint has been removed, babies catch-up or catch-down to their genetic growth potential if they have an optimal post-natal environment.

Figure 21: Multivariate regression analysis of the predictors of child underweight in selected countries of Asia and Latin America

Predictors	Criterion: Child Underweight		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
Constant	66.372	105.557	22.468
Ln pubexphlth	-.421 (-3.878)**		
Adult Literacy	-.629 (-5.787)***		
Ln animal protein		-0.669 (-6.853)***	-.332 (-3.012)**
USIH		-0.246 (2.555) *	
Sanitation		-0.272 (-3.160)**	
LBW rate			0.500 (4.951) ***
Anaemia Pregnancy			0.264 (2.981) **
Adjusted R ²	.693	.847	.886
F	32.638	44.737	60.586
P	<0.001	<0.001	<0.001
N	28	19	23

^aStandardized Beta coefficients with their t test scores (in brackets).
^{*}p<0.05, ^{**}p<0.01, ^{***}p<0.001
^a ln pubexphlth, ln pubexphlth, sece nro, tele visi, adu liter, gdp.
^b ln pubexphlth, adu liter, ln animal prot, mea sev ac, ln feseccnro, dpt, con trac ept, less dollar, ln doctor, sanitat ion, usih, protcpd, calpcpd.
^c ln pubexphlth, , adu liter, ln animal prot, sanitat ion, usih, lbw , a nem preg.

14.4 Discussion points:

Strategies for preventing LBW that have focused on interventions during pregnancy, such as dietary supplementation, have only achieved modest reductions in LBW and have not had any beneficial long-term effects for the mother or baby.

The evidence on the importance of maternal age, anthropometry and socio-economic status in determining LBW seems to support the need for interventions to be targeted at improving the health of women of reproductive age. In a number of developing countries, many pregnancies occur in teenage girls who are still growing and are at greater obstetric risk than other women. It is important that interventions consider these factors. It is possible that upstream interventions, including those that target maternal education, would have the potential to reduce teenage pregnancy in developing countries.

15. SUMMARY OF CONSENSUS ISSUES AND RECOMMENDATIONS TO ADDRESS GAPS IN THE EVIDENCE

15.1 Consensus issues

15.1.1. Low birthweight has long been used as an indicator of adverse fetal outcome. Although it should continue to be measured and reported to permit

comparisons with historical data, it is an inadequate indicator for 2 reasons: first, it does not distinguish between short gestation (preterm birth) and restricted fetal growth (IUGR), and second, it is a dichotomous measure that does not permit assessment of the entire gestational age or fetal growth (e.g. birthweight for gestational age) distributions.

- 15.1.2. Preterm birth and IUGR are important to the extent that they affect important outcomes in the fetus/infant, child, and adult. The outcomes affected include mortality, morbidity, growth, development, and quality of life in infancy and childhood, and perhaps over the entire life course.
- 15.1.3. IUGR and preterm birth are both multifactorial in etiology, and it is unlikely that interventions directed at single risk factors will have major impact on their prevention at the population level.
- 15.1.4. Maternal body size and energy intake have major impacts on fetal growth. Maternal height and pre-pregnancy BMI have large, robust, and probably causal associations with birthweight for gestational age and the risk of IUGR. Maternal overweight and obesity, however, are associated with an increased risk of stillbirth. Famine and food shortages have been shown to sharply reduce fetal growth. Energy supplementation, on the other hand, has been demonstrated to modestly increase mean birthweight and shift the fetal growth distribution to the right, but to substantially reduce the risk of IUGR; it may also reduce the risk of stillbirth and neonatal death. These benefits have been achieved in carefully controlled and monitored research studies, but no convincing evidence has emerged of comparable benefits of universal or targeted public health food supplementation programs, although several such large-scale programs are currently under evaluation.
- 15.1.5. The importance of maternal micronutrient status for fetal growth or gestational duration has not been clearly demonstrated. Randomized trials of individual vitamins or minerals have not shown benefit for these outcomes, although prevention of adverse maternal (e.g. anaemia) and other fetal (e.g. neural tube defects) outcomes are clear. Randomized trials of multiple micronutrient supplementation are currently in progress, and their results are eagerly awaited.
- 15.1.6. The negative effects of maternal cigarette smoking, malaria (in primiparae), genito-urinary tract infection, and pre-eclampsia on fetal growth and/or gestational duration are well established. Effective interventions have been identified to reduce the adverse effects of some, but not all, of these etiologic risk factors, although the potential benefits and risks of these interventions for the mother have been inadequately studied.

15.2 Gaps and recommendations

Gap 1:

Better data are required about the gestational age distribution and incidence of preterm birth in developing country settings. This will require early identification of

women who have missed their menstrual periods and/or use of early ultrasound dating, at least on a regional basis or in representative population-based samples.

Recommendations: A review should be carried out to establish what is currently known in this area, to point out inconsistencies or problems with the data currently available and to highlight what should be done to address these issues. Recommended action on improving data collection and quality should address practical issues including cost-effectiveness, outcomes and ethical issues.

The reviewers who carry out this work should also give their views, based on interpretation of the evidence, relating to how readily and in what time scale the recommendations could be implemented.

Gap 2:

Better data are required on the fetal growth (birthweight, length, and head circumference for gestational age) distribution and body composition among populations living in favourable environmental circumstances in a variety of developing country settings. This will provide crucial knowledge about achievable targets for size at birth in these settings, as well as suggest hypotheses to explore the reasons for differences in these distributions across settings in both developing and developed countries. It will also help resolve the dilemma as to whether different reference standards should be used in different geographic settings.

Recommendations: This gap will partly be informed by the fetal component of WHO work on 'Development of Growth Reference Data for International Applications from Fetal Life to Childhood'. The objective of this work is to review strategies for fetal growth monitoring and the need and methodology for development of fetal growth reference data for international applications. The background literature review for this work will inform this gap in the evidence.

Gap 3:

A review of the evidence is needed to understand how variations in fetal growth and gestational duration affect fetal, infant, child, and adult health outcomes, and whether the magnitude of those effects differs in different settings.

Recommendations: The review should focus on determining how the risks associated with preterm birth and IUGR vary in terms of setting and according to cause within setting. The risks and benefits associated with shifting the birthweight distribution in different settings should be assessed.

This work should include assessment of the evidence on the relationship between maternal body size and fetal size. This is important in determining risk of adverse outcomes associated with low birthweight, since low birthweight infants of small mothers may well have lower risks of adverse outcomes associated with their birthweight than other low birthweight infants. The evidence for other potentially modifying factors (e.g. altitude, maternal age, parity, and pre-eclampsia) should also be examined.

Although a great deal is known about the relationship of fetal growth to adult outcomes (e.g. cardiovascular disease), it will be important to ensure that what is already known is collated and briefly reviewed so that it can be considered by the meeting of experts. For the work on earlier outcomes, there will need to be a similar collation and brief review of evidence on what is already known, with emphasis on identifying areas where further research is needed.

Gap 4:

A review of temporal (including inter-generational) trends in fetal growth and gestational duration in countries that have undergone major economic growth in the recent past (e.g. Japan, Singapore, and Thailand) could shed important light on the extent to which gains in these outcomes are achievable, and the time scale over which the gains can occur. Conversely, close study of temporal trends in the former Soviet Republics may provide important information about the adverse effects of short-term economic decline.

It was agreed that gap 4 should also include a review of trends in upstream issues, such as maternal education and income, and the impact that changes in these may have had, for example in parts of Latin America, such as Cuba and Costa Rica, and in parts of Asia (e.g. Sri Lanka).

Gap 5:

More information is required about the effects of several potential risk factors for reducing fetal growth and shortened gestation, because these risk factors are highly prevalent in some developing countries. These include congenital syphilis and rubella, indoor smoke exposure, heavy maternal work, maternal anaemia and iron deficiency, and such maternal diseases as HIV/AIDS, sickle cell disease, and non-malarial parasitic diseases.

Gap 6:

Previous research and interventions have focused too narrowly on “downstream” individual-level risk factors and too little on “upstream” societal factors that impact on individual women. Such upstream factors include poverty, inadequate maternal education, and early adolescent pregnancy. The downstream focus may explain the disparity between the relatively modest benefits of specific clinical interventions demonstrated in randomized trials and the large differences between countries, between socio-economic or ethnic groups within countries, and within populations or population subgroups over time.

Recommendations: A review of the evidence on effectiveness of interventions at both downstream and upstream levels is needed. It should also summarise the evidence bearing on targeted versus “across-the-board” intervention strategies. The review should assess the evidence relating to maternal outcomes as well as to pregnancy and fetal outcomes. Recommendations should be action orientated, reporting cost, feasibility and timescales.

Gap 7:

Although research on energy supplementation has shown only modest effects on low birthweight, there are a number of large-scale public health nutritional programmes that are ongoing. A review of these nutritional programmes should be carried out in order to assess their impact on low birthweight.

Gap 8:

The evidence on benefits (and possible risks) of fetal growth monitoring and its impact on pregnancy outcomes should be reviewed. This should include assessment of different approaches to monitoring, for example serial measurements of maternal weight, fundal height measurements, and ultrasound, and should include recommendations for desirable changes in these measures during pregnancy.

Gap 9:

Previous trials of micronutrient supplementation have focused on immediate pregnancy outcomes rather than longer-term outcomes. The evidence on the impact of maternal micronutrient status on low birthweight should be reviewed in order to identify gaps in the evidence and make recommendations for future research. For example, there is insufficient evidence on the relationship of maternal iron deficiency anaemia to iron stores and anaemia in the fetus and to longer-term infant/childhood outcomes such as growth, cognitive development, and chronic diseases of adulthood.

Gap 10:

Reliable, population-based data on major pregnancy outcomes are required in developing country settings, at least on a regional, random sentinel, or periodic basis. These data are essentially for comparing countries and regions among each other and within countries and regions over time and provide an essential underpinning for managing maternal and child health services and programmes at both the clinical and public health policy levels. A review should be undertaken to suggest how such data can be obtained on a population-wide basis, even if restricted to certain regions or to randomly-selected “sentinel” sites, and how the data can be used for health care planning, targeting interventions, and research.

References

1. Graafmans WC, Richardus JH, Borsboom GJ, et al. Birth weight and perinatal mortality: a comparison of "optimal" birth weight in seven Western European countries. *Epidemiology* 2002;**13**:569-74.
2. World Health Organization. Maternal Anthropometry and Pregnancy Outcomes. *Bull World Health Org* 1995;**73** (Suppl).
3. Villar J, Farnot U, Barros F, Victora C, Langer A, Belizan JM. A randomized trial of psychosocial support during high-risk pregnancies. The Latin American Network for Perinatal and Reproductive Research. *N Eng J Med* 1992;**327**:1266-71.
4. Prentice AM, Whitehead RG, Watkinson M, Lamb WH, Cole TJ. Prenatal dietary supplementation of African women and birth-weight. *Lancet* 1983;**1**:489-92.
5. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998;**351**:1477-82.
6. Kramer MS. Balanced protein/energy supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*. Oxford: Update Software, 2000.
7. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet* 1999; **354**:`955-61.
8. Stephenson T, Symonds ME. Maternal nutrition as a determinant of birth weight. *Arch Dis Child Fetal Neonatal Ed* 2002;**86**:F4-F6.
9. World Bank. *Curbing the Epidemic: Governments and the Economics of Tobacco Control*. Washington: The World Bank, 1999.
10. Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. *Paediatric and Perinatal Epidemiology* 1997;**11**:140-51.
11. Lechtig A, Shrimpton R. What relevance for child survival and development? In: *Prenatal and Perinatal Biology and Medicine, Vol 1*. London: Harwood Academic Press, 1987.
12. Yip R, Scanlon K, Trowbridge F. Improving growth status of Asian refugee children in the United States. *JAMA* 1992;**267**:937-40.
13. Vangen S, Stoltenberg C, Skjærven R, Magnus P, Harris JR, Stray-Pedersen B. The heavier the better? Birthweight and perinatal mortality in different ethnic groups. *Int J Epidemiol* 2002;**31**:654-660.
14. Margetts BM, Yusof SM, Al Dallal Z, Jackson AA. Persistence of lower birthweight in second generation South Asian babies born in the United Kingdom. *J Epidemiol Community Health* 2002;**56**:684-687.
15. Shrimpton R. *Multivariate regression analysis of the predictors of child underweight in selected countries of Asia and Latin America*. 2003 (UnPub)



MEETING OF ADVISORY GROUP ON MATERNAL
NUTRITION AND LOW BIRTHWEIGHT
Geneva, 4 – 6 December 2002

Annex 1

List of Participants

Dr Fernando Barros
Centro Latino Americano de Perinatología (CLAP OPS/OMS)
Hospital de Clinicas, piso 16
Casilla de Correo 627
11000 Montevideo, Uruguay
Tel: +598 2 487 2929
Fax: +598 2 487 2593
Email: BARROSF@clap.ops-oms.org

Dr Michael Kramer
Department of Paediatrics and of Epidemiology and Biostatistics
McGill University
Faculty of Medicine
1020 Pine Avenue West
Montreal, Québec H3A 1A2, Canada
Tel: +1 514 934 4400
Fax: +1 514 989 3753
Email: michael.kramer@mcgill.ca

Dr Catherine Law
Environmental Epidemiology Unit
Medical Research Council
Southampton General Hospital
GB-Southampton SO16 6YD
United Kingdom
Tel: +44 23 8077 7624
Fax: +44 23 8070 4021
Email: claw@mrc.soton.ac.uk

Dr Andrew M. Prentice
MRC International Nutrition Group
Public Health Nutrition Unit
London School of Hygiene and Tropical Medicine
49-51 Bedford Square
GB-London WC1B 3DP
Tel: +44 207 299 4682
Fax: +44 207 299 4666
Email: Andrew.Prentice@lshtm.ac.uk

**MEETING OF ADVISORY GROUP ON MATERNAL NUTRITION AND LOW
BIRTHWEIGHT**

Geneva, 4 – 6 December 2002

List of Participants (cont'd.)

p. 2

Dr Roger Shrimpton
Honorary Research Fellow
Centre for International Child Health, Institute of Child Health
University College London
4, Badger Wood Walk
GB- York, YO10 5HN, United Kingdom
Tel: +44 1904 410 931
Fax: +44 1904 438 891
Email: rshrimpton@btinternet.com

Other Agencies

Dr Venkatesh Iyengar
Nutritional and Health-Related Environmental Studies Section
Division of Human Health, Department of Nuclear Sciences and Applications
International Atomic Energy Agency (IAEA)
Wagramer Strasse 5, P.O. Box 100
A-1400 Vienna, Austria
Tel: +43 1 2600 21657
Fax: +43 1 26007
Email: [V. Iyengar@iaea.org](mailto:V.Iyengar@iaea.org)

**MEETING OF ADVISORY GROUP ON MATERNAL NUTRITION AND LOW
BIRTHWEIGHT**

Geneva, 4 – 6 December 2002

List of Participants (cont'd.)

p. 3

WHO Secretariat

Nutrition for Health and Development (NHD)

Dr Graeme A. Clugston

Director

Tel: +41 22 791 3326

Fax: +41 22 791 4156

Email: clugstong@who.int

Dr Sultana Khanum

Tel: +41 22 791 2624

Fax: +41 22 791 4156

Email: khanums@who.int

Dr Bruno de Benoist

Tel: +41 22 791 3412

Fax: +41 22 791 4156

Email: debenoistb@who.int

Dr Mercedes de Onis

Tel: +41 22 791 3320

Fax: +41 22 791 4156

Email: deonism@who.int

Dr Janis Baird (Temporary Adviser)

Environmental Epidemiology Unit

Medical Research Council

Southampton General Hospital

GB-Southampton SO16 6YD

United Kingdom

Tel: +44 23 8076 4052

Fax: +44 23 8070 4021

Email: J.BAIRD@soton.ac.uk

Reproductive Health and Research (RHR)

Dr Jelka Zupan

Tel: +41 22 791 4221

Fax: +41 22 791 4189

Email: zupanj@who.int

**MEETING OF ADVISORY GROUP ON MATERNAL NUTRITION AND LOW
BIRTHWEIGHT**

Geneva, 4 – 6 December 2002

Provisional List of Participants (cont'd.)

p. 4

Evidence and Information for Policy (EIP)

Dr Claudia E. Stein

Tel: +41 22 791 3234

Fax: +41 22 791 4909

Email: steinc@who.int

Child and Adolescent Health and Development (CAH)

Dr José C. Martines

Tel: +41 22 791 2634

Fax: +41 22 791 4853

Email: martinesj@who.int

Noncommunicable Disease Prevention and Health Promotion (NPH)

Dr Pirjo Pietinen

(former staff member)

Nutrition and Noncommunicable Disease Prevention (NNP)

Mrs Kristin Thompson

Tel: +41 22 791 3485

Fax: +41 22 791 1581

Email: thompsonk@who.int

Tobacco Free Initiative (TFI)

Ms Annemieke Brands

Tel: +41 22 791 3463

Fax: +41 22 791 4832

Email: brandsa@who.int



**MEETING OF ADVISORY GROUP ON MATERNAL
NUTRITION AND LOW BIRTHWEIGHT**
Geneva, 4 – 6 December 2002

Annex 2

Agenda

Wednesday, 4 December

Morning

09h00

Welcoming remarks

Dr Graeme A. Clugston, Director,
Department of Nutrition for Health and Development

Objectives of the Meeting

Dr Sultana Khanum
Department of Nutrition for Health and Development

Introduction of Participants

Nomination of Chairperson

Introductory remark: Relationship between low birthweight, preterm birth, intra-uterine growth retardation and their relationships to child survival, health, growth and later morbidity/mortality

Professor Michael Kramer, McGill University, Canada

Background and overall framework for project (pre-circulated)

Professor Michael Kramer

Terms of reference of the group and plan for the meeting

(pre-circulated)

Framework for knowledge gathering and analysis

(pre-circulated)

10h30 – 10h45

COFFEE

What is the nature of evidence and how can we use it?

Presentation by Dr Catherine Law,
Medical Research Council (MRC), UK
General discussion

12h30 – 14h00

LUNCH

Afternoon

What are we trying to achieve – prevention of low birthweight or a wider improvement in fetal growth?

Presentation by Dr Catherine Law
General discussion

15h30 – 15h45

TEA

MEETING OF ADVISORY GROUP ON MATERNAL NUTRITION AND LOW BIRTHWEIGHT

Geneva, 4 – 6 December 2002

page 2

Wednesday, 4 December

Afternoon (cont'd.)

What determines optimal fetal growth/LBW

Presentation by Professor Michael Kramer

General discussion

Thursday, 5 December

Morning

What interventions might be employed to promote fetal growth/prevent LBW?

Presentation by Dr Andrew Prentice,

London School of Hygiene and Tropical Medicine (LSHTM), UK

General discussion

10h30 – 10h45

COFFEE

How do the issues vary between different settings and populations?

Presentation by Dr Fernando Barros,

Centro Latino Americano de Perinatología (CLAP), Uruguay

General discussion

12h30 – 14h00

LUNCH

Afternoon

What are the possible timescales for action?

Presentation by Dr Roger Shrimpton,

Centre for International Child Health, Institute of Child Health (ICH), UK

General discussion

15h30 – 15h45

TEA

Review first 2 days and plan for final day

Friday, 6 December

Morning

Conclusions on main issues

Agreeing the scientific framework, and planning for its completion

10h30 – 10h45

COFFEE

Recommendations for action

Next steps

CLOSURE



Knowledge gathering and analysis: Framework

Introduction

The aim of this phase is to gather evidence which will answer questions needed to inform the development of a strategy i.e. to action. The first question to be addressed is the aim of the strategy. Should this be to prevent low birthweight as currently defined, to prevent reduced growth using some other definition, or to define and try to promote an optimal level of fetal growth? (Much of the available literature will focus on low birthweight (LBW) <2500 grams.) The framework below uses the terms “optimal fetal growth” and “low birthweight or LBW” to include all these options. The influence of duration of gestation should be considered in relation to each question.

Background

Definition of problem, including consideration of what we mean by the terms size (and weight) and growth, and the part gestation plays in these.

Size of problem, including issues of data quality and availability

Variation by country/region, population, setting

Questions to be asked

What are we trying to achieve for fetal growth?

What growth is too little (and also too much)? Is there evidence for thresholds or particular shapes of the fetal growth distribution?

What are we trying to achieve from optimal fetal growth/prevention of LBW:

ie what outcomes are we trying to influence?

mortality/longevity/burden of disease

health related quality of life

non-health related quality of life

developmental status

significant health related behaviours

and when do those outcomes occur?

immediately and in infancy

in childhood

in adolescence

in adulthood

How is fetal growth best measured - by attained size at birth, by body proportions or composition, by the trajectory of fetal growth?

Is optimal growth/LBW the same for all populations, or does it differ by genetic background, gender, setting or culture?

What is the contribution of gestation to optimal fetal growth/LBW? (See attached table as an example.)

What determines optimal fetal growth/LBW?

Focusing on modifiable factors (and how modifiable).

Genetics	Nutritional	Maternal size and characteristics	Diseases	Pregnancy complications	Maternal lifestyle	Environment
Genetics factors and gene environment interactions Paternal size Sex	Timing of the effect: During pregnancy In adolescence (and before pregnancy) Childhood - protein and energy - micronutrients - famine Inter-generational issues Setting: severe, moderate or no malnutrition on population basis	Uterine capacity Multiple births Parity Birth spacing	Infections of public health importance: - malaria - anaemia - syphilis - rubella - other?	Eclampsia Pregnancy infection Preterm birth	Smoking Alcohol intake	High altitude Pollution Socio-economic factors

What is the size of these associations (in relative and absolute terms)? Is there information, which will allow their contribution to be calculated?

What heterogeneity is there?

Does the evidence suggest causality?

Interventions

What interventions are known to promote optimal fetal growth/prevent LBW?

Nutritional

Health care

Health related behaviour

Infection control

(Do we need to include post-natal interventions?)

How much difference will they make (in relative and absolute terms)?

What is the cost-effectiveness of each intervention?

Are interventions accepted and valued by mothers/parents?

Cross cutting themes

Several issues cut across the questions above. They include;

- The influence of the settings in which people live, the population group from which they come, and other characteristics that they have.
- The different timescales and points in the life course when fetal growth may be influenced, interventions applied, and over which a strategy might operate.
- The nature of the evidence, its methodology and availability, and the importance of the gaps in the evidence in presenting a barrier to a strategic approach.

Further details are given under each heading below

Settings/populations

Is optimal growth/ a meaningful definition of LBW the same in all settings and for all populations? Are these different, for example, for boys rather than girls, by race or by setting e.g. in developing countries versus those in transition? From this, are universal fetal growth curves useful/appropriate?

What is the balance of relative and attributable risk for the determinants in different populations/settings?

What is the merit and value of different interventions in different settings?

What views do mothers/parents/ advocates have on these interventions and the values of different outcomes, and how do these vary by setting and population?

Timescales

What action could be taken now, during this generation (20 years), in the long-term (50 years i.e. 2-3 generations)?

What are the secular trends in fetal growth, its determinants, and the outcomes we are trying to influence?

When do we want to act in the lifecourse, before conception, during pregnancy, during infancy and childhood, during adolescence, during adult life (excluding peri-conceptually)?

When do mothers/babies want to reap the benefits: immediately, during childhood, in adult life?

What is the nature of the evidence and how can we use it?

What are the different types of evidence and what can they tell us?

What are the methodological issues?

How can we best consider all consequences of action, including the possibility of doing harm?

What are the gaps in the evidence and how can they be filled?