

**WHO Technical Consultation towards the Development of a  
Strategy for Promoting Optimal Fetal Development**

Geneva, 25–27 November 2003

## Annex 1

### **Summaries of the background papers**

#### **Paper 1: Maternal nutrition and low birth weight**

Low birth weight (LBW) defines a heterogeneous group of infants, some of whom will be growth restricted, some of whom will be born early, and some of whom will be both born early and growth restricted. A better understanding of the mechanisms that influence each of these outcomes, in particular those that improve health outcomes for the individual in the longer term, is critical for optimizing fetal development.

Studies have revealed the existence of a strong positive association between maternal pre-pregnancy nutritional status and a woman's ability to nourish her growing foetus. Nutritional interventions during pregnancy appear to modify this association by altering the rate of fetal growth, although the extent of the modification is usually modest in terms of birth weight. The reasons for the limited impact of dietary modification during pregnancy are not yet fully understood, the main areas of difficulty being an inability to completely unravel the causal pathway between maternal nutrition (whether cumulative or dietary) and fetal nutrition, and a limited knowledge of the effect of peri-conceptual nutrition on later fetal growth.

Many determinants of fetal growth are established prior to pregnancy, either in the immediate peri-conceptual period and/or during the life-course of the mother (including her own intrauterine development). Recent evidence suggests that peri-conceptual undernutrition might be important in setting the length of gestation. To date, most trials have investigated post-conception interventions involving only single micronutrients, when in reality the majority of undernourished women suffer from multimicro- and macronutrient imbalances.

The burden of LBW in the world remains high, with the greatest numbers of low-birth-weight infants being born to women from developing countries, where the main cause of LBW at delivery is reduced fetal growth rate. Addressing this problem in the long term may have more to do with improving the nutritional status of, and food availability to, women throughout their life-course, rather than implementing short-term pregnancy interventions. A focus on nutritional solutions, however, ignores the social and cultural context in which maternal dietary deficiencies tend to arise and the coexisting problems, including poverty and infection, which allow them to proliferate.

## **Paper 2: The developmental origins of adult disease**

Low birth weight has been linked with increased rates of adult coronary heart disease and related disorders, including stroke, hypertension and non-insulin dependent diabetes. These associations have been extensively replicated in studies in different countries. As they tend to be dependent on lower birth weights in relation to the duration of gestation (rather than to the effects of a pre-term birth), this is thought to be a reflection of slow or impaired fetal growth. Moreover, the associations are graded and extend across the normal range of birth weights, i.e. infants weighing 7 pounds are lower risk for heart disease than infants weighing 6 pounds, and those weighing 9 pounds are lower risk than those weighing 8 pounds.

The observed link between impaired fetal development and an increased risk of coronary heart disease in adulthood is thought to be a consequence of *developmental plasticity*, a term used to describe the phenomenon by which one genotype can produce a range of different physiological or morphological states depending on responses to different environmental conditions during development. Recent observations suggest that slow growth in infancy and rapid childhood weight gain can exacerbate the negative effects, in terms of risk of adult heart disease, of slow prenatal growth.

Based on evidence obtained from the study of the association between low birth weight and risk of adult coronary heart disease, a new vision of optimal early human development, which takes account of both short- and long-term outcomes, is now emerging. According to current thinking, coronary heart disease and related disorders arise through a series of interactions between environmental influences and the pathways of development that precede them. Thus these diseases are the product of branching development pathways, which are triggered by the environment both before and after birth.

Maternal influences (e.g. body composition, dietary balance), are known to have long-term effects on adult disease, without necessarily affecting size at birth. For instance, several studies have demonstrated that underweight women are more likely to have infants that go on to develop a resistance to insulin in adulthood, an association that can only be partly attributed to a low birth weight.

### **Paper 3: Optimal fetal growth and size at birth**

Optimal fetal growth occurs when there is no pathological impediment to fetal growth or to the length of gestation. Various factors determine these two variables: some are physiological (e.g. the size of the mother, birth order, sex, ethnicity), others are pathological (e.g. infections, cigarette smoking, diabetes, hypertension).

Perinatal mortality is usually higher at the low extremes of birth weight and gestational age. However, population-specific variations in fetal growth rate and in the length of gestation can also influence perinatal mortality adversely. In Fiji, for example, rates of stillbirths are higher among ethnic Indians than in ethnic Fijians. In most populations, optimum birth weight, i.e. the birth weight category with the lowest perinatal mortality, is much higher than the mean birth weight. Furthermore, the optimum birth weight in the population generally increases as the mean birth weight increases.

Since accurate gestational age estimates are not always available, especially in developing countries, birth weights, or more specifically birth weight distributions are more commonly used to explore associations between perinatal mortality and birth size. In many populations, the distribution of birth weight tends to be skewed towards lower birth weights. In addition, the size of the residual distribution (the excess area under a skewed distribution curve relative to one that is “normal” or bell-shaped) appears to be linked to infant survival. When the residual distribution is small (i.e. the birth weight distribution curve is symmetrical and there is little skewing as is the case in Japan), infant mortality is low; conversely, the larger the residual distribution, the greater the neonatal mortality rate. This form of analysis can be used in most situations, either to compare the association between the magnitude of the residual distribution and infant mortality across different populations or to examine trends over time in the same population.

There is no universal reference for birth weight or for fetal growth that fits all fetuses, irrespective of setting. Population history and, to a lesser extent perhaps, ethnicity are nevertheless important determinants of fetal growth and

size at birth. While ethnicity may be considered to be a marker for socioeconomic influences in some settings with multi-ethnic populations, this may not always be valid assumption in more ethnically homogeneous populations.

In the absence of universally applicable references, a reference distribution for birth weight should be developed for different populations and ethnic groups based on observations of low-risk healthy pregnant women and their fetuses and neonates. Adjustments should be made for any physiological factors that are known to influence fetal size and growth, such as birth order (first-born infants are smaller than second or later-born infants) and sex (male infants are heavier than female infants). Although birth weight references are often called fetal growth curves, they are in fact not the same thing. Whereas the birth weight references are based on actual birth weights, fetal growth curves are derived from sonographic estimations of fetal weights (i.e. measurements taken while the baby is still in the womb). Also, it is important to note that since pre-term births are usually associated with intrauterine growth restriction, birth weight standards do not reflect true fetal weight at earlier periods of gestation.

In both developed and developing countries, birth weight distributions change over time. It is therefore important to periodically review population data for temporal changes in birth weight distributions and revise existing references. Whereas the negative effects of famine and undernutrition on birth weight are relatively well known, available data on intergenerational changes in birth weight among immigrant populations from developing countries are conflicting.

#### **Paper 4: Determinants of fetal growth**

In developing countries, intrauterine growth restriction (IUGR) is part of the cycle of undernutrition underpinned by poverty, lack of safe water and high prevalence of specific and non-specific infections. Once pregnancy is established, low gestational weight gain plays a major role in the impairment of fetal growth. Whereas the evidence linking micronutrient deficiency or specific nutrient imbalances to poor fetal growth is weak, there is increasing evidence to suggest that physically demanding work during pregnancy, highly prevalent among women in developing countries, may contribute to IUGR. Pregnancy-induced hypertension, particularly when associated with proteinuria, is another important determinant, along with malaria and HIV (in areas where these infections are highly prevalent). In many developing

country settings, adolescent pregnancy, especially in still-growing girls, is also an important contributor to poor fetal growth.

Maternal undernutrition exerts its influence mainly through the stunting of growth during the mother's childhood, which leads to short stature and a low pre-pregnancy weight, especially when combined with frequent diarrhoeal episodes because of poor sanitation and a lack of safe water. In addition to undernutrition during childhood, maternal birth weight also has a bearing on fetal growth; if a mother was herself a small baby, she is more likely to produce small babies. Although as yet its effects on embryonic and fetal growth are poorly understood, the quality of the peri-conceptual diet is considered to be another important determinant of fetal growth.

In developed countries, impaired fetal growth is less prevalent, but it nevertheless remains associated with adverse health outcomes throughout the life-course. Smoking is currently the largest single known determinant of IUGR in developed countries. Low gestational weight gain and pregnancy-induced hypertension are also believed to play a role, whereas physically demanding work, physical abuse and passive smoking are all emerging as possible contributors to poor fetal growth. Intergenerational and early childhood influences, working through low maternal birth weight and poor growth in early childhood (secondary to relative undernutrition), contribute to impaired fetal growth mainly by their effects on maternal height and pre-pregnancy weight. Despite the absence of the severe poverty that characterizes many developing countries, poor social circumstances during the mother's childhood, and immediately before and during pregnancy, underpin many of the above factors that impact on fetal growth.

While interventions directed at individual pregnant women may help to improve fetal growth, in both developing and developed countries societal-level interventions aimed at reducing the proportion of women of child-bearing age who are stunted and underweight at conception are likely to have the greatest global impact on fetal growth. Such interventions are likely to be expensive but the costs of implementation are balanced, and may even be outweighed, by the short- and long-term costs of continuing high levels of fetal growth impairment.

## Annex 2

### **Objectives and expected outcomes**

#### **Objectives**

- 1) To determine current knowledge on what constitutes optimal fetal development from population to individual perspective;
- 2) To review the causes of sub-optimal fetal development and low birth weight as a proxy indicator on population level;
- 3) To review the effects that sub-optimal fetal development has on morbidity, disability and mortality across the life course;
- 4) To review (cost-) effective interventions to ensure optimal fetal development by type of interventions and their timing;
- 5) To advise WHO on the next steps towards strategy development for optimal fetal development.

#### **Expected outcomes of the meeting**

1. A report of the meeting, summarizing the background information, discussions and recommendations;
2. Recommendations on next steps for WHO to develop the strategy.

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## Annex 3

### Agenda

#### Tuesday, 25 November

08:30 – 09:00 **Registration**

09:00 – 09:45 **Opening**

*Dr Joy Phumaphi,  
Assistant Director-General, Family and Community Health*

**Background and objectives**

*Dr Sultana Khanum*

**Optimal size at birth**

*Dr Jelka Zupan*

09:45 – 10:30 **Nutrition and low birth weight** (Plenary)

*Prof Andrew M. Prentice*

10:30 – 11:00 COFFEE BREAK

11:00 – 12:30 **Nutrition and low birth weight** (cont.)

*Prof Andrew M. Prentice*

12:30 – 14:00 LUNCH

*12:45 – 13:30 Lunchtime Seminar (Salle D)*

**Levels of Low Birth weight**

**Latest UNICEF/WHO Estimates and Methodology**

**Dr Ann Blanc, Consultant to UNICEF**

14:00 – 15:30 **The developmental origins of adult disease** (Plenary)  
*Prof David J.P. Barker*

15:30 – 16:00 TEA BREAK

16:00 – 17:30 **Optimal fetal growth and size at birth** (Plenary)  
*Prof Matthews Mathai*

17:30 – 18:00 **Wrap up**  
*Chairperson*

18:00 – 19:30 **Reception** (*Crystal Restaurant – WHO Cafeteria*)

### **Wednesday, 26 November**

09:00 – 10:30 **Factors determining fetal growth** (Plenary)  
*Prof Nicholas J. Spencer*

10:30 – 11:00 COFFEE BREAK

11:00 – 11:15 **Introduction of Working Groups**

11:15 – 12:45 **Working Groups – Session 1** (Allocated rooms)  
*Objective 1:*  
To determine current knowledge on what constitutes optimal size at term birth from the public health perspective.

12:45 – 14:00 LUNCH

14:00 – 15:30 **Reporting from the Working Groups** (Plenary)  
*Rapporteur of Working Groups*

15:30 – 16:00 TEA BREAK

16:00 – 17:30 **Working Groups - Session 2** (Allocated rooms)  
*Objective 2:*  
To review the causes of sub-optimal size at term birth and low birth weight as a proxy indicator on population level;

*Objective 3:*

To review the effects that sub-optimal size at birth has on morbidity, disability and mortality across the life course;

*Objective 4:*

To review (cost-) effective interventions to ensure optimal size at term birth by type of interventions and their timing.

### **Thursday, 27 November**

09:00 – 10:30 **Reporting from the Working Groups** (Plenary)  
*Rapporteur of Working Groups*

10:30 – 11:00 COFFEE BREAK

11:00 – 12:30 **Working Groups - Session 3** (Allocated rooms)

*Objective 5:*

To advise WHO on the next steps towards strategy development for optimal size at term birth

12:30 – 14:00 LUNCH

14:00 – 15:30 **Reporting from the Working Groups** (Plenary)  
*Rapporteur of Working Groups*

15:30 – 16:00 TEA BREAK

16:00 – 17:30 **Next steps**

**Conclusions and closing of the Consultation**

*Dr Sultana Khanum*