

PROMOTING OPTIMAL FETAL DEVELOPMENT
Report of a Technical Consultation



**World Health
Organization**

**Nutrition for Health and Development/Making Pregnancy Safer/
Evidence and Information for Policy**

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Strategy for Promoting Optimal Fetal Development**

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Executive summary

Background

A Technical Consultation was held in November 2003 to discuss the development of a strategy to promote optimal fetal growth and development. This meeting followed an earlier preliminary examination, held in December 2002, at which the focus of discussion had been the need to develop a strategy to reduce the prevalence of low birth weight. It was decided at that meeting that, as an indicator of fetal development, birth weight has certain limitations. Firstly, it excludes consideration of a range of factors that contribute to fetal development, but which are not necessarily manifested in birth size. It also ignores other aspects of early life that are important once survival is secured, for example, cognitive development. Furthermore, it disregards the effects of adverse influences or beneficial interventions on aspects of maternal health and well-being, and thus artificially separates maternal and child health. Thus, although its usefulness as a single measure for identifying problems of public health significance was not disputed, the notion of low birth weight was nevertheless believed to be both too non-specific and too narrow when considering the wider aspects of function and health.

Recent advances in knowledge about the impact of early life events on the neonatal transition, infant development, cognitive development and life-long sequelae means that a broader characterization of the outcome of pregnancy is needed rather than birth size alone. The issue of concern thus became the need to *optimize fetal development*, a concept which embraces a broad set of considerations including the health of the mother before and during pregnancy; the length of gestation; the size of the newborn for his or her gestational age; whether fetal development has been disrupted; and whether the infant is exposed to a nutritional, physical and emotional environment that maximizes its potential for growth, development and a healthy life. Accordingly, birth is seen as a single event in a continuum of development and change that starts at or before conception and extends into adulthood, and in which earlier experience can have effects on subsequent function throughout all stages of the life-cycle.

The global burden of death and disability as a result of impaired fetal development is huge. Although the burden is particularly high in developing countries, it is also a significant concern in developed

countries. The promotion of optimal fetal development should result in improved outcomes for early and later survival, morbidity and other measures of human capital. This in turn will enhance population social and economic health and well-being.

Securing optimal fetal development requires the potential mother to be in a state of physical and emotional health prior to and during her pregnancy. For a mother to adequately support the development of a fetus, she must be able to provide it with sources of sufficient energy and a suitable mix of nutrients. Her ability to meet the needs for fetal development is not related in a simple way to her current or immediate past dietary intake, but is dependent on her general state of health, in particular, her emotional and physical health status, and her health behaviours before and during pregnancy (i.e. smoking, alcohol, drug use and sexual practices).

Health care for pregnancy and delivery

It was the considered opinion of the Consultation that the first and immediate priority is to ensure that adequate baseline health care is provided for all mothers and children according to current WHO guidelines. The ability of a woman to carry a healthy pregnancy and successfully suckle her infant during its first year of life requires that she has the capacity to provide all the energy and nutrients that are required. Any ill health (including chronic illnesses that continue during pregnancy and acute illnesses or complications that arise during gestation) will compromise and limit this ability, to a greater or lesser degree. Therefore, it is axiomatic that in order to achieve a successful pregnancy and a healthy infant, attention must be given to the provision of basic health care and obstetric facilities (i.e. evidence-based antenatal care and safe delivery by a trained birth attendant). Any ongoing constraints in these health-care systems will undermine any further attempts to optimize fetal development, and thus fail to meet the fundamental rights of the child.

Distribution of size at birth

Growth and development are characterized by an increase in size, progressive structural complexity and maturation of function. It is a highly organized process in which complex changes are coordinated sequentially in time, and changes at the molecular and cellular level are integrated to enable development of the whole organism. Any adverse

influence on the process can have consequences at later times, the extent of which will depend upon the nature, timing, duration and severity of the perturbation. Two crude measures of fetal growth are the duration of gestation and the weight of the newborn for its gestational age. A low birth weight baby is one that weighs less than 2500 g at birth. As growth is a progressive process, a baby may weigh less than 2500 g at birth because it is born too soon, or because it is small for its gestational age.

Low birth weight has been widely used as an indicator of perinatal health. However, there are limitations to using birth weight as a key index of perinatal health, problems that are highlighted by the fact that in some settings rates of infant mortality are falling without concomitant changes in birth weight. Moreover, because it does not distinguish between a shortened gestation and sub-optimal fetal growth and because many antenatal factors can impact on subsequent health without affecting birth size, it is an imperfect indicator of fetal development. A broader set of indices of fetal development is therefore desirable. These could include, for instance, maternal status at the beginning of and during pregnancy, measures of the length of gestation, birth size, perinatal mortality and morbidity, and measures of infant growth and morbidity. Such measures should, however, be interpreted within the context of the relevant population and their use supported by a better understanding of the relationships between those factors which determine poor physical growth and those which determine the risk of ill-health.

Substantial differences in mean birth weights exist within populations, and also between populations. The factors that determine the differences in birth weight within populations are not necessarily the same as those which operate between populations. Therefore, there is a need to determine the nature of the factors that contribute to poor growth and development before birth, both within and between populations, and the extent to which they are amenable to specific interventions. The possible adverse effects of interventions also require further exploration. For example, a short-term increase in fetal size would theoretically increase the incidence of cephalo-pelvic disproportion and could thereby augment obstetric risk to mother and baby. There is some evidence that exaggerated catch-up growth postnatally may not necessarily be optimal for long-term health outcomes for those born to a compromised pregnancy.

Nutritional status during pregnancy

Growth is characterized by the net deposition of tissue, which inevitably requires the ready availability of energy and nutrients. The mix of nutrients that is required for tissue formation is not fixed, but varies as the early conceptus matures from an embryo into a fetus and eventually an infant. The source of available nutrients also varies over time: initially nutrients are derived from within the newly fertilized egg, then from within the milieu of the maternal reproductive tract, and subsequently via the placenta or human milk. At each stage the demands for growth and development change, as does the pattern of nutrients available. Ultimately all nutrients will have been derived from the maternal diet, but the pattern of nutrients consumed by the mother will be very different to the mix that is available to the fetus, and moreover very different to the mix that is required by the fetus to meet its immediate needs for growth. Nutrient availability thus depends upon the nature and size of maternal reserves and her metabolic capability to establish a nutrient environment which is suitable for a particular stage of development.

Interestingly, studies in which single nutrient supplements have been provided during pregnancy to improve fetal growth have generally been unsuccessful, but women who possess a good nutritional status at the time they become pregnant are better able to meet the demands imposed by the pregnancy and have more successful outcomes. Short women and women who are thinner or fatter than normal at the time of conception are at increased risk of giving birth to babies of sub-optimal size for their age and (in the case of thin women) of a pre-term birth.

Meeting the nutritional needs of pregnancy places a metabolic demand on the mother. Her ability to meet this demand will in part be determined by the extent to which there are other concurrent demands competing for the same resource. In the teenage mother who has not yet completed her own growth, there is clear competition between the needs of her own body and her ability to support the growth of the fetus. Hard physical labour also increases the demand for nutrients: in addition to the extra nutritional energy demands, the postural effects associated with load bearing may compromise the blood flow to the uterus, thereby limiting the availability of nutrients to the placenta and fetus. Many women experience stress, either mental stress brought on by the pressures of their experiences in life, or because of exposure to infections or the effect of lifestyle choices, such as smoking or consumption of alcohol. Each of these stress factors can have an adverse effect on a woman's nutritional

status, by increasing nutrient losses from the body, by changing the availability of nutrients within the body, or by altering appetite and the amount and pattern of food consumed. Multiple pregnancies increase the amount of nutrients that have to be delivered over the course of a single pregnancy, and a short inter-pregnancy interval limits the opportunity for the repletion of nutritional reserves between successive pregnancies. All of the above-mentioned factors, acting directly or indirectly, have been shown to impair the opportunity for the fetus to grow and develop normally. Many tend to be more common in socially and financially deprived groups of women, and their presence will increase the risk of sub-optimal development and ill-health (in the both the short and longer term) in the newborn infant.

Improving maternal nutritional status is not simply a question of improving the pattern of dietary intake. What is required is an improvement in the ability of the body to utilize effectively the available nutrients for their appropriate purpose. Attempts to improve nutritional status should recognize that this can be achieved in a number of ways, not all of which require a change in dietary consumption patterns. In other words, interventions other than diet-based ones can improve fetal nutrition. For example, reducing maternal workload will improve the nutritional status of a mother, as will measures to reduce the prevalence of malaria.

The importance of timing

The combination of observations made on infants conceived through in vitro fertilization and experimental observations which indicate maternal nutrition at conception can influence the length of a pregnancy, suggests that greater attention should be paid to the peri-conceptual period. Although the potential impact of other factors such as environmental toxins, workload and stress (acting directly or through nutritional status) during this period is poorly documented, recent advances in developmental biology, in particular, our growing understanding of the capacity of environmental factors operating in early development to have lasting effects on fetal health (through epigenetic processes), adds weight to the idea that the peri-conceptual period is an especially important one for interventions to optimize maternal health and thereby confer benefit to the next generation.

Embryogenesis is largely determined in the first trimester. During this time, the developing embryo is exquisitely sensitive to environmental factors; the effects of toxins, infections (such as rubella) and nutritional factors (e.g. folate or iodine deficiency) on organogenesis are well recognized. There is increasing evidence that more subtle environmental influences may also influence the outcome of pregnancy during this period.

Once the placenta is fully established, fetal growth and development is dependent on the integrity of the maternal-placental unit and is heavily influenced by maternal stress, workload, metabolic energetics and general health. Infections such as malaria interfere with placental function and thus impair fetal growth. In this regard, the role of toxins such as drugs of abuse, ethanol and tobacco is also well established, as is the risk of pre-term delivery due to ascending infection and low-grade inflammation. Abuse, overwork and poor nutrition can all exert an influence on late gestational fetal growth and possibly increase the risk of pre-term birth.

In both developed and developing countries, maternal and infant outcomes are heavily dependent on the quality of intrapartum care. The presence of a trained caregiver is vital. Pre-delivery triage to ensure appropriate levels of care can do much to reduce the risks of death, infection and bleeding for the mother, and the risks of death and of peripartum asphyxia and consequent encephalopathy for the baby.

The health of the neonate is greatly influenced by its maturity and size. It is also dependent on the quality and hygiene of intrapartum care, the establishment of breastfeeding and the quality of parental investment in that infant. At this stage, environmental factors start to influence the quality of cognitive development. All of these factors are in turn governed by the health of the mother. The health of the *mother-infant dyad*, a relationship that extends from conception well into childhood, requires close surveillance in the first days and weeks after birth to detect and treat infection and lactation failure, and to promote and support exclusive and prolonged breastfeeding, and a stimulating emotional environment for both mother and child.

Conclusion

There can be no doubt that early life events have a critical impact on survival, quality of life and human capital. Improvements in fetal development that go well beyond a focus on low birth weight, will have a major impact on early and later survival, morbidity and on other measures of human capital. These will be self-sustaining, promote social and economic health and well-being, and thus benefit all societies. The development of a strategy to promote fetal development will therefore be in close accord with the Millennium Development Goals. Some components of such a strategy have the potential to achieve an immediate impact, for example, reductions in the prevalence of adolescent pregnancy. The benefits of other interventions applied to young children at the present time will only be realized as they grow into adults who are better able to support an optimal pregnancy.

Although there has been value in using low birth weight to highlight a public health problem, the measure is limited in its application and is, in certain circumstances, misleading. Optimal fetal development requires the mother to be in a state of physical and emotional health both prior to and during her pregnancy. Maternal nutritional status is an important determinant of the outcome of a pregnancy, but this embraces wider considerations than current dietary intake alone. There are other social and behavioural factors that clearly impair fetal development, such as maternal smoking, malaria and HIV/AIDS, and which must be addressed in any strategy that seeks to optimize fetal development. Maternal age, size, general health and workload can also have an impact on fetal development; these risk factors need to be considered within a broader context, one that embraces a mother's education, her socioeconomic status and food security. Consideration of all such factors is integral to developing a holistic strategy.

The Consultation considered that a holistic strategy was both necessary and desirable. If an effective strategy were implemented, its effects would likely influence a plethora of outcomes throughout the life-cycle, for example, improved school performance and skills; improved health in infancy, childhood and adolescence; improved health for the next generation of mothers and their fetuses; improved health in adult life; increased productivity and economic gains; and a reduced disease burden at all stages throughout life. Information to support strategy development is already available, although some of it needs to be collated and analysed. There are also some gaps in core knowledge which need to be

addressed. Despite this, available data allow the immediate development of an integrated strategy for the optimization of fetal development for global application. Some elements can be derived by improving coordination between existing programmes such as Making Pregnancy Safer and Roll Back Malaria.

1. Introduction

A WHO Technical Consultation met in Geneva during the period 25–27 November 2003. The meeting, which was opened by Dr J. Phumaphi, Assistant Director-General, Family and Community Health, on behalf of the Director-General, was convened as a follow-up to a previous meeting held in December 2002 at which the focus of discussion had been the need for a strategy to reduce the prevalence of low-birth-weight infants.

The primary objective of the present meeting was to review current knowledge relating to the measurement, causes and consequences of sub-optimal fetal growth and development, as well as available information on interventions that promote optimal fetal development. The main findings, summarized in this report, form part of an extended programme of work, the longer term aim of which is the adoption of a resolution on promoting optimal fetal development during the Fifty-ninth World Health Assembly to be held in 2006.

During the first half of the meeting, four commissioned background papers were presented and discussed. These papers covered the following topics: maternal nutrition and low birth weight; developmental origins of adult disease; optimal fetal growth and size at birth; and factors which determine fetal growth. Summaries of the background papers can be found in Annex 1. The second part of the meeting was dedicated to group work during which participants were asked to reach conclusions with regard to what they believe constitutes sub-optimal fetal development, what are its causes, its effects and its outcomes, and which interventions promote optimal fetal development. Finally, participants were asked to suggest what the next steps towards the goal of formulating a global strategy for optimal fetal development should be. The full set of meeting objectives and expected outcomes is attached to this report as Annex 2, and the meeting agenda is itemized in Annex 3.

Although the burden of death and disability due to impaired fetal development is particularly high in developing countries, it is also a significant concern in many developed countries (1, 2). By taking steps to promote optimal fetal development, it should be possible to improve outcomes not just for early survival but also for later survival, morbidity and other measures of human capital, which in turn, will lead to improved social and economic health and well-being. In other words,

investment in the ability of all mothers to carry a health pregnancy will not only have immediate personal and social benefit, but also cumulative benefit for personal and social health and development over many decades and is the rationale for the development of the present strategy.

Optimal fetal development requires the potential mother to be in a good state of physical and emotional health both prior to, and during, her pregnancy. Furthermore, to adequately support the development of her fetus, a mother must be able to provide it with sufficient energy and a suitable mix of nutrients. Current research indicates that a woman's ability to meet the needs for fetal development is not related in any simple way to her current or immediate past dietary intake, but is rather more dependent upon her general state of health. It thus follows that factors other than patterns of dietary consumption at conception and throughout pregnancy determine a mother's ability to nourish her fetus and it is these factors that are the determinants of pregnancy outcomes. For instance, a mother who becomes pregnant at an early age, before she has completed their own growth, has a limited ability to nourish her fetus. Similarly, women who have poor obstetric support, suffer from infection(s), adopt undesirable personal behaviour or experience a challenging social environment are less likely to complete a healthy pregnancy. Within the wider context in which a pregnancy takes place, the quality and capability of health-care delivery systems will determine to a large extent the ability of a woman to carry a healthy pregnancy. In striving for optimal fetal development, the first and immediate priority is then the provision of adequate baseline health care for all mothers and children according to current WHO guidelines (3).

2. Shifting the focus: from birth weight to fetal development

At the earlier preliminary meeting, discussion had centred on the need to develop a strategy to reduce the prevalence of low-birth-weight infants. However, the consensus view that emerged from the December 2002 meeting (4) was that a focus on low birth weight as an indicator of fetal development is potentially misleading, because it excludes consideration of a range of important factors that contribute to fetal development but which are not necessarily manifested in birth size. Such a focus also ignores other aspects of early life which are important once survival is secured, for example, cognitive development. Furthermore, it disregards the effects of adverse influences or beneficial interventions on various

aspects of maternal health and well-being, and thus artificially separates maternal health from child health. Although the concept of low birth weight has been useful as a single measure for identifying problems of public health significance, it was nevertheless considered to be both too non-specific and too narrow when used as an indicator of wider aspects of biological function and health. For this reason it was agreed that it would be more appropriate to work towards a strategy that had as its goal the *optimization of fetal development* in the broadest sense of the term. This represents a significant shift in focus from the original intent, i.e. the development of a strategy for optimizing birth weight.

The concept of optimal fetal development embraces a broad set of considerations including:

- the health of the mother before and during pregnancy;
- the length of gestation;
- the size of the newborn for his or her gestational age;
- whether fetal development has been disrupted and whether the infant is exposed to a nutritional, physical and emotional environment that maximizes its potential for growth, development and a healthy life.

According to this paradigm, birth is viewed as a single event in a continuum of development and change that starts at or before conception and extends into adulthood, and in which earlier experience can have effects on subsequent function throughout all stages of the life-cycle.

3. Indicators of fetal development

Fetal growth and development are characterized by an increase in size, progressive structural complexity and maturation of function. It is a highly organized process in which complex changes are coordinated sequentially in time, and changes at the molecular and cellular level are integrated to enable development of the whole organism. Any adverse influence on this process can have consequences at later times, the extent of which will depend upon the nature, timing, duration and severity of the perturbation. Since weight at birth marks several aspects of the fetal development process and because it is relatively easy to measure, birth weight (together with information on rates of perinatal mortality) has been used extensively for many years in comparative statistics as the primary proxy indicator of improved perinatal health. A low-birth-weight infant is defined as one that weighs less than 2500 g at birth, and the duration of a normal pregnancy is taken to be around 40 weeks from the

first day of the last menstrual period. As growth is a progressive process, a baby may weigh less than 2500 g at birth either because it is born too soon, or because it is small for its gestational age.

There is a wide range of birth weights within any given population and also substantial differences between populations in mean birth weights. For instance, a baby weighing 2.8 kg at birth would be considered to be relatively heavy in countries such as Bangladesh or India, but relatively light in say, Sweden. The factors which determine the differences in birth weight within populations are not necessarily the same as those which operate between populations (5). Within populations, those at the extreme lower or upper end of the birth weight distribution are considered to be at increased risk of ill-health, but the nature of the main causative factors, and the extent to which they are amenable to intervention, varies markedly between populations (6). There is a need to understand more fully the nature of the factors that contribute to poor growth and development before birth, both within and between populations, and the extent to which these are associated with differences in health outcomes.

Birth weight is strongly related to maternal stature (7). Women who are short have smaller babies, a finding which cannot be explained by recognized genetic factors alone (8, 9 Kramer, 1987; Wilcox et al., 1995). Women who are extremely thin are also more likely to have smaller infants. Birth weight can be improved in thin women who are able to increase their body weight during pregnancy. Nevertheless, there is no simple relationship between a mother's dietary consumption and size at birth. Studies in which single nutrient supplements have been provided during pregnancy to improve fetal growth have generally been unsuccessful, and in some circumstances have even indicated adverse consequences (10)). What studies have established is that women who have better nutritional status at the time they become pregnant are better able to meet the demands imposed by the pregnancy, and tend to have more successful outcomes. Some caution has to be exercised when attempting to increase the average birth weight of a population, given the possibility of an increased incidence of cephalo-pelvic disproportion and consequently a greater obstetric risk to both mother and baby.

3.1 Limitations of birth weight as an indicator of optimal fetal development

Despite its undisputed value as a public health indicator, birth weight does not capture all aspects of fetal growth and development (11). As an indicator of optimal fetal development, birth weight is thus somewhat limited. The main reasons for this are: firstly, it does not distinguish between a shortened gestation and sub-optimal fetal growth and secondly, many antenatal factors can impact on subsequent health outcomes without affecting birth size. In particular, birth size is not a good indicator of brain development; there are several factors that operate during pregnancy which can impair the development of the fetal brain but which do not necessarily influence birth size, cocaine exposure being one example. Associations of this nature are not yet fully understood and highlight the need for more research to unravel the relationships between those factors that determine poor physical growth and those that determine risk of ill-health.

The following apparent paradox highlights some of the problems associated with using birth weight alone as an indicator of improved perinatal health. In many populations small, but potentially important, reductions in the length of gestation (which result in a reduction in mean birth weight) have been observed. Furthermore, in all but perhaps the most deprived societies, there has been an increase in the survival of infants born at shorter gestations, and a fall in stillbirth rates. Consequently, in several countries, for example Brazil, Canada and the United States, perinatal mortality has continued to decline despite a rise in the number of pre-term births, i.e. births before 37 completed weeks of gestation (which results in a greater proportion of smaller babies in the population). Thus in situations where the rates of infant mortality are falling without concomitant changes in birth weight, the use of birth weight alone would fail to identify an improvement in perinatal health (12). The picture is further complicated by the fact that for some situations adverse effects on fetal development are associated with increased birth weight: for example, the infant of a mother who is pre-diabetic is likely to be larger than normal, but at an increased risk of ill-health (13).

Similar difficulties are encountered when comparing societies that differ in their average family size. The effect of parity on birth size is well recognized, with the first born being relatively smaller than the second or third born (14). In societies where there is a trend towards a greater

frequency of first-born babies, such as those in China and some parts of Europe, the distribution of birth weights will be shifted towards lower birth weights relative to that in countries that have a mixture of family sizes. Under such circumstances, the use of birth weight as the sole indicator of perinatal health could lead to erroneous conclusions.

3.2 What constitutes optimal fetal development from a public health perspective?

Optimal fetal development can be defined as that state at birth in which the neonate is most likely to survive and thrive through the neonatal transition and infancy, and to be prepared such that early developmental effects do not impact negatively on the individual's life-course. It also must take account of the mother's health because an infant is more likely to thrive if its mother is healthy. Ideally then, measures of optimal fetal development should characterize a process that lasts from conception to birth and beyond. Early experiences continue to exert some influence on growth and development during lactation, later in infancy and childhood, and even on health during adult life. For instance, there is increasing evidence to suggest that sub-optimal fetal development can have lifelong and intergenerational consequences in terms of the risk of certain diseases (see section 4 and Annex 1).

There is no single indicator that can be used to characterize sub-optimal development, and thus the magnitude of the burden of impaired fetal development. Since there may not be a consistent relationship between birth weight and outcomes such as infant mortality, nor with many features of sub-optimal fetal development which relate to the risk of multiple adverse outcomes later in life, birth weight alone is clearly an inadequate measure. However, there is every reason to argue for the ongoing collection of good quality data on birth weight; despite its limitations, it does provide a clearly quantifiable indicator of some (albeit not all) aspects of fetal development. Every effort should thus be made to ensure that all babies are weighed as reliably as possible at birth.

In the absence of a single suitable measure, an alternative approach would be the adoption of a broader set of indices of fetal development, which could be interpreted within the context of the relevant population. The spectrum of indicators that could be used to measure optimal fetal development includes: maternal body mass index (BMI); weight in early and late pregnancy; stillbirths; gestational age; birth defects (especially

neural tube defects); placental weight; perinatal mortality; early neonatal mortality; infant mortality; maternal mortality; birth difficulties and/or operative interventions in pregnancy; wasting and stunting at birth (restricted fetal growth); infant head circumference; maturity (rates of prematurity); neonatal morbidity (including asphyxia and respiratory distress syndrome); and infant morbidity. Potentially useful postnatal indicators of fetal development include growth indicators at 6 months and 1 year (i.e. indices of wasting and stunting). While it is recognized that sub-optimal fetal development has important effects on cognitive development, these are more difficult to measure reliably in public health settings.

The complexity of the spectrum of fetal development measures collected would depend on the setting, their intended purpose and the availability of resources. There is a difference between the level of information needed to support research (and thus guide and structure policy), and that which is required for monitoring and evaluating health-care programmes. Generally speaking, research is more demanding in terms of the complexity and frequency of observations that are required, but where resources allow, data that supports a wide range of indices could be gathered as a matter of routine. Although collecting data for a broad spectrum of indicators may not be feasible in all situations, every effort should be made to monitor as broad a set of indicators as possible in sentinel populations in order to demonstrate their value at the population level.

Perhaps the most critical aspect to consider is how might the way in which these indices are measured be improved in practice, and, in terms of the application of raw data, how their use as statistics be made more effective. Birth weight should be viewed as the minimum amount of information to be collected for all births. In addition, gestational age (maturity) should be measured using early ultrasound (i.e. at < 20 weeks) in sentinel populations whenever possible. Where direct measurements are not possible then estimates based on the date of the last menstrual period should be used to indicate the length of gestation. If the only measure available is birth weight, then residual distributions should be calculated (see Annex 1). Every effort should be made to also record fetal presentation and multiple pregnancies.

4. Effects of sub-optimal fetal development

As our knowledge of developmental biology expands, there is greater awareness that events early in human development can impact on the later stages of life. Even a seemingly modest primary event can have much greater consequences at a later stage of development. The discovery that in experimental situations a modest change in nutritional exposure during the peri-conceptual period can induce epigenetic changes in genes leading to modification in their expression throughout the life of the animal is a dramatic example; this phenomenon is sometimes called fetal metabolic programming (15, 16). Epigenetic changes can also occur in response to non-nutritional influences, such as maternal nurturing behaviour (17). More recently, research has focused on the potential functional capability of the individual at birth, that is to say, on the capability of an individual to cope effectively with the transition to an independent existence, to thrive in infancy and childhood, and to grow optimally, and in the case of the female, her ability to become a successful mother, something which may or may not be reflected in birth size.

Increasingly, the weight of evidence points to the fact that the beneficial effects of improved fetal development and a healthy start to life exerts an ongoing influence on a plethora of outcomes throughout the entire life-course of an individual. These benefits include:

- improved school performance and skills;
- improved health during adolescence especially among girls;
- improved health in adult life;
- improved physical work capacity;
- improved learning skills;
- increased productivity and economic gains;
- reduced burden of infectious diseases;
- reduced burden of obesity and non-communicable diseases including type II diabetes, hypertension and cardiovascular disease.

Evidence that sub-optimal development can have life-long and intergenerational consequences in terms of the risk of certain diseases is steadily mounting. The consequences of high birth weight have also attracted attention in recent years, although this is still an area of research that requires further investigation. Not only has very high birth weight been associated with an increased risk of mortality, but it is also believed to contribute to subsequent obesity, cancer and other chronic diseases (18).

For many populations, the optimal birth weight is greater than the mean birth weight for a number of outcomes. For infant mortality, the optimum birth weight may be 350 g greater than the mean birth weight. Similar relationships have been shown for other outcomes, for example, for IQ, diabetes, cerebral palsy and learning difficulties (19–21). This has important policy implications as it suggests that a small upwards shift in the distribution of birth weights is likely to have a much larger benefit for the whole population, not just for the relatively few who are at the extremes of birth weight (22). For instance, if the relationships between cognitive function and birth weight are similar to those between infant mortality and birth weight (i.e. the optimum birth weight for cognitive function is greater than the mean), then any improvement in birth weight will produce a sizeable benefit in terms of better cognitive function in the population, and in turn in terms of poverty reduction.

5. Causes of sub-optimal fetal development

The processes leading to sub-optimal fetal development are more likely to be the result of an interaction of multiple factors than any single cause. The list of factors that have the potential to interact in this way is quite extensive, and is presented in **Table 1**. The relative importance of these causal factors will vary among women, being dependent on the local environment. However, the most important higher level cause is deprivation in its widest sense, most particularly the failure to ensure adequate support to protect the health of a mother, before, during and after her pregnancy.

5.1 Nutritional status

Growth is characterized by the net deposition of tissue, which inevitably requires the ready availability of energy and nutrients. The mix of nutrients that is required for tissue formation is not fixed, but varies according to developmental stage, i.e. as the early conceptus matures from an embryo to a fetus and eventually an infant. The source of nutrients also varies over time; initially nutrients are derived from within the newly-fertilized egg, and then from within the milieu of the maternal reproductive tract. Subsequently, they are delivered via the placenta or via human milk. At each stage the nutritional demands for growth and development change, as does the mix of nutrients available. Ultimately, all nutrients will have been derived from the maternal diet, but the mix of

nutrients consumed by the mother will be very different to the mix that is available to the fetus, and, moreover, very different to the mix that is required by the fetus to meet its immediate needs for growth. Thus, nutrient availability will depend upon the nature and size of maternal reserves and her metabolic capability to establish a nutrient environment that is suitable for each particular stage of development.

Meeting the nutritional needs of pregnancy places a metabolic demand on the mother. Her ability to meet this demand will in part be determined by the extent to which there are other concurrent demands competing for the same resource. In a younger mother who has not yet completed her own growth, there is clear competition between the nutritional needs of her own body and those of her growing fetus (24, 25). Hard physical labour also increases a woman's nutritional requirements; in addition to the extra energy and nutrient demands, the postural effects associated with load bearing can compromise the blood flow to the uterus, thereby limiting the availability of nutrients to the placenta and fetus. Multiple pregnancies increase the demand for nutrients over the course of a single pregnancy, whereas a short inter-pregnancy interval limits the opportunity for the repletion of nutritional reserves between successive pregnancies. Various stressors can also have an adverse effect on a woman's nutritional status and ability to carry a good pregnancy. Stress factors, which might include mental stress brought on by the pressures of life experiences, exposure to infections and/or various lifestyle behaviours (e.g. smoking, consumption of alcohol), exert their effect on nutritional status by increasing nutrient losses from the body, by changing the availability of nutrients within the body, or by altering appetite and the amount and pattern of food consumed (8, 26). One possible, but nevertheless important, consequence of a mother needing to cope with a range of environmental stressors is that a diet which might appear adequate for a normally healthy individual may not be appropriate or adequate for women in whom altered demands lead to an altered nutritional state.

All of the above-mentioned risk factors, acting either directly or indirectly, have been shown to impair the opportunity for the fetus to grow and develop normally. Many of these factors tend to be more common in socially and financially deprived groups of women, and their presence will increase the likelihood of the newborn infant being at greater risk of sub-optimal development and thus ill-health in the short and longer term (27). On the other hand, women who are in better health and have better nutritional status at the time they become pregnant are

better able to meet the demands imposed by the pregnancy, leading to more successful outcomes.

Interventions to improve nutritional status need to recognize that improving the nutritional status of a potential mother is not simply a question of improving the pattern of dietary intake, but require the broader consideration of improving the ability of the body to utilize effectively the available nutrients for their appropriate purpose. This can be achieved in a number of ways, not all of which rely on the need to change or improve the diet. For instance, improving the environment, reducing infection risk and decreasing work load can all achieve significant improvements in nutritional status for the same dietary intake (28) and should be seen as an integral part of nutritional intervention strategies where appropriate.

Despite recent advances in our understanding of nutritional factors in pregnancy (see Annex 1), further work is needed in order to fully appreciate the complex interactions among those factors which impair a mother's ability to meet the uneven nutrient demands of pregnancy. In particular, there is a need to better understand how access to maternal nutrient reserves might be modulated by an adverse environment, thereby leading to constraints on fetal development.

5.2 Environmental and intergenerational factors

Evidence is mounting that the health of a woman is influenced by her experiences as a fetus and that these experiences influence her functionality during her own pregnancies. Certainly, the egg that will go on to form her own fetus first forms when the mother herself is an early embryo in her mother's uterus. It thus follows that each individual is influenced by the environment during the first trimester of his or her maternal grandmother's pregnancy.

Several studies have demonstrated that the birth weight of a mother and infant pair are highly correlated. This has been attributed to differences in the growth of the female reproductive tract in women who are born small, which in turn influences the growth of the next generation as fetuses. It is probable that a woman's metabolism is influenced by antenatal programming when she herself was a fetus (29–31). Although well described in the animal literature, there is, however, less evidence for such intergenerational effects from human populations.

It has been suggested that the pace of intergenerational change in humans may well determine the rate at which a society can pass through the demographic, environmental and nutritional transition without exposing itself to the risk of increased frequency of those diseases which have been associated with life-style changes. Thus for many groups, vastly improved social circumstances and access to better diets may take place within a single a generation, but the biological capability to cope with, and adapt to, the richer environment takes more than a single generation. This “mismatch” between biological capability and opportunity is thought to lie behind much of the observed increases in the prevalence of chronic disease in societies in transition (32).

Table 1
Potential causes of sub-optimal fetal development by category, and possible interventions

Category	Cause	Intervention	Timing of intervention	Comments
Genetic factors	Race/ethnicity Haemoglobinopathies Other genetic disorders Thrifty genes hypothesis	Pre-natal screening Genetic counselling	Pre-conception	Major research gaps on importance.
Maternal characteristics	Small stature/size Composition Age Parity Pregnancy interval Metabolic competence Uterine size and blood flow New partner Duration of cohabitation	Policies to promote empowerment of women, including prevention of domestic violence Policies to prevent pregnancies at a very young age	All ages All ages	“Upstream” policies are not specified as these are not directly under WHO influence but will be country/region specific.
Nutrition	Energy balance (macro-/micronutrient) Body composition Weight gain/over weight Iron deficiency/anaemia Antioxidants Amino acid pattern and supply Retinoids Dietary lipids (e.g. docosohexaenoic acid) Placental hypertrophy	Improve nutrition of women who are likely to conceive (including women who are undernourished and obese) Promoting food security and access to food Promote prolonged exclusive (6 months) breastfeeding Prevention of iodine deficiency	Setting specific (e.g. at marriage, menses/cohabitation) Pregnancy Postpartum Pre-and during pregnancy Postpartum	Do not supplement with: — nutrient low foods; — high protein foods; — single nutrients except with evidence of deficiency.
Diseases	Infectious diseases (e.g. bacterial vaginosis, HIV/AIDS, malaria, tuberculosis, rubella, syphilis/parasites) Inflammation Urinary tract infection Endometriosis Diabetes Metabolic syndrome Polycystic ovary syndrome Morning sickness	Prevention of HIV Malarial control (i.e. intermittent preventive treatment, insecticide treated bed nets, case Mx) Access to appropriate health care	Pre-pregnancy Pregnancy All ages	

Category	Cause	Intervention	Timing of intervention	Comments
Pregnancy complications	Pregnancy-induced hypertension Impaired glucose intolerance Depression Hyperemesis Bleeding haemorrhage Placenta previa Corticosteroid treatment	WHO focused antenatal care package Skilled attendant at delivery, Prevention of mother-to-child transmission Bellagio package ^a plus sleeping position Neonatal package	Pregnancy Intrapartum Intrapartum Postpartum	Knowledge gaps 1. Treatment/prevention of bacterial vaginosis in developing world 2. Burden of infection
Maternal life-style	Stress Smoking/alcohol/drugs Single motherhood Physical activity/workload Sleep duration/rest Number of partners Late pregnancy intercourse	Policies to reduce physical workload Prevention of smoking, alcohol and substance misuse	Pre- and during pregnancy Pre- and during pregnancy	
Environment	Family size Exposure to pollutants (e.g. smoke (indoor pollution), toxicants, heavy metals) Occupational hazards Drinking water Built environment Social support Education Maternal self-esteem Access to health care	Reduction of poverty Education of women (and girls) Access to appropriate health care	All ages	“Upstream” policies are not specified as these are not directly under WHO influence but will be country/region specific. “Food for education” is an example of a programme to improve nutrition and education.

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The Bellagio Group on Child Survival have identified 23 cost-effective interventions that, if universally implemented, could prevent up to two thirds of deaths in the under-fives, currently estimated at nearly 11 million per year (23).

The Bellagio Group on Child Survival have identified 23 cost-effective interventions that, if universally implemented

6. Potential interventions

Unfortunately, concrete evidence relating to the effectiveness of interventions aimed at reducing the prevalence of low birth weight is limited. There have been few randomized controlled trials of specific interventions in populations where the problems of low birth weight are especially prevalent. Even fewer studies have explored in a formal way the impact of a package of interventions designed to improve pregnancy outcomes. Such studies are necessarily complex and thus difficult to design and expensive to carry out.

It is useful to distinguish two types of interventions. *Firstly, there are interventions that aim to make the environment optimal for the potential mother to nurture her fetus; these tend to be public health interventions. Secondly, there are interventions that aim to maximize the role of an individual woman as an environment for her fetus; these tend to be clinical interventions.* Any specific intervention, or package of interventions, will not necessarily achieve both aims. More significantly perhaps, given that one consequence of sub-optimal fetal development is likely to be a lifelong increased risk of ill-health, reducing the risk in later life of chronic diseases (at least for diseases that have fetal programming as an underlying cause), may require interventions which exert their influence during the earliest stages of the peri-conceptual period.

Despite the apparently complex nature of the relationships between maternal health before and during pregnancy and fetal growth and development, evidence suggests that interventions can be effective, even when applied as single interventions in specific situations. For example, all the interventions listed at the end of Table 1 (i.e. those relating to maternal lifestyles and environmental risk factors), are likely to lead to an improved environment and healthier behaviour, and will help to make sure that mothers who get pregnant are better able to support optimal fetal development. During pregnancy, interventions that reduce nutritional and other stress factors on the mother, such as the effective diagnosis and treatment of silent infection, almost certainly also have the potential to confer a benefit.

Some concern has been expressed that under certain circumstances improved fetal growth could have adverse consequences for the mother. This is most likely to arise in the case of adolescent mothers who have

not yet completed their own growth; in addition to an increased risk of nutritional competition, there is also a greater risk of cephalo-pelvic disproportion at delivery. Any measures that are intended to promote optimal fetal development should therefore be integrated with efforts aimed at making pregnancies safer. Similarly, in settings where infections such as HIV/AIDS and malaria are prevalent, it is vital that planned interventions are coherent and complementary.

In terms of a package of interventions for promoting optimal fetal development, *the first and foremost priority is to ensure that adequate baseline health care is provided to all mothers and children. The ability of a woman to carry a healthy pregnancy and successfully suckle her infant during its first year of life requires that she has the capacity to effectively provide all the necessary energy and nutrients.* The ability of a woman to do this is a fundamental marker of good health; any ill-health (including chronic illnesses that continue through pregnancy and acute illnesses or complications that arise during gestation) compromises this ability to a greater or lesser degree. *It is therefore axiomatic that in order to achieve a successful pregnancy and a healthy infant, attention must be given to the provision of basic health care and obstetric facilities according to current WHO guidelines (i.e. provision of evidence-based antenatal care, safe delivery by a trained birth attendant, close surveillance of mother and infant in the early postnatal period).* Any ongoing constraints in these basic health-care systems will limit the effectiveness of nutritional approaches to enhance maternal and child health and undermine attempts to optimize fetal development, and as such represent a failure to meet the fundamental rights of the child.

Although it is advantageous to the mother if interventions are delivered as components of an integrated package, in practice the delivery of maternal health care and the delivery of child health care are not always coordinated at the level of health-care facilities as effectively as they might be. The current emphasis on the importance of securing optimal fetal development underscores the need to ensure that services for both maternal health and nutrition and those for infant and child care are indeed delivered in an integrated and coordinated manner. However, explicit recognition that maternal and child health care should be provided as a coordinated service is still lacking; programmes such as Integrated Management of Childhood Illness (IMCI) on the one hand and Making Pregnancy Safer on the other could be made even more effective if a more integrated approach to the provision of maternal and child health care were to be adopted.

Adoption of a more coherent and integrated approach, i.e. one which ensured that the care and support of the mother and child was provided as a single coordinated service, offers several advantages for health-care services in many developing countries, especially as such a policy is more likely to protect fetal and infant development. Although the application of current knowledge could have great impact, so far it has been difficult to make significant progress in this area. Constraints operate across all settings in both developing and developed countries, for mothers-to-be, pregnant mothers, lactating mothers and their babies. There are a number of reasons for this, which cover a wide range of experience and embrace considerations of a structural, political and sociological nature. Although the notion of integrated services makes much practical and economic sense in the decentralized delivery of health services, in that it allows the possibility of increased impact for the same resources, it is acknowledged that coordination and integration can appear less attractive centrally.

There will of course be differences between populations and regions in the causes of sub-optimal fetal development, which will be of significance when planning the most suitable specific or more general packages of interventions. For example, in populations where fetal growth restriction is prevalent (e.g. in the Indian subcontinent), risk factors for maternal stunting and how best to manage these, will be especially important considerations. Where current nutritional status is obviously poor, interventions designed to improve nutrition prior to conception are likely to be high on the agenda. In sub-Saharan Africa, particular attention will need to be paid to the issue of how best to address problems related to the high prevalence of malaria, HIV/AIDS and other infections during pregnancy.

6.1 A life-cycle approach to intervention

In the interests of providing a complete and integrated package of health care for securing optimal fetal development, it is important to recognize that the ability of a woman to carry a good quality pregnancy is a reflection of her accumulated health experience throughout her own development and secondly, that earlier interventions have the greatest likelihood of leading to more firmly established benefits in the longer term. Thus, a strategic life-cycle approach to health-care provision, i.e. one that seeks progressive improvement in health between successive

generations and recognizes that investment in health at a period remote from pregnancy itself may be critical in ensuring optimal pregnancy outcomes, should be invoked. To this end, six life-stages are identified: childhood and adolescence, pre-pregnancy and the peri-conceptual period, early pregnancy, mid and late gestation, the peri-partum period, and the neonatal period and beyond. Intergenerational factors also require consideration and can be considered to be a seventh stage in a life-cycle approach. Clearly the nature and magnitude of the benefits of interventions will depend on investment priorities at different stages of the life-cycle. Specific interventions limited to the period of pregnancy itself, for instance, may have some immediate effects but investment in more general strategies (e.g. improving the growth and education of young girls and women) may have less obvious effects in the short term on immediate outcomes, but will have a major impact over a more prolonged period. Factors operating at each stage of the life-cycle, and their relevance to specific interventions, are discussed in more detail below.

6.1.1 Childhood and adolescence

The growth of women is strongly influenced by their health as an infant, as a child and as an adolescent. Stunting impacts the next generation and is influenced by nutritional status, workload and infection risk. Pregnancy outcome is strongly influenced by the age of the mother and whether she is fully grown when she conceives (24). The age at first pregnancy is largely determined by cultural and societal factors; where there is a greater level of investment in the education of young girls and women and in their empowerment, the timing of first pregnancies tends to be delayed and the relative importance of adverse cultural factors tends to diminish.

6.1.2 Pre-pregnancy and the peri-conceptual period

Some data suggest that fetal growth and development are influenced by the nutritional and health status of the mother in the period before she conceives and her state of health at the time of conception. If this is the case, there will be major challenges for planning interventional and preventive programmes. Given that only a minority of the total number of pregnancies worldwide are prospectively planned, there is a very strong argument for a global focus on the health of all women of reproductive age if pregnancy outcomes are to be improved. Both the general nutritional state of women, as indicated by their height and weight (33) and their specific micronutrient status (e.g. folate, iron, vitamin A, fatty acids) are likely to be critical in this period. The growing

recognition of the role of epigenetic change, together with evidence obtained from observations made on infants conceived through in vitro fertilization, suggests that particular attention needs to be paid to the peri-conceptual period. Although the potential impact of other factors such as exposure to environmental toxins, heavy workload and stress (acting directly or indirectly through nutritional status) during this period is relatively poorly documented, the accumulated weight of evidence, particularly that from the field of developmental biology, points to the peri-conceptual period as being an especially important time for interventions which optimize maternal health and thereby confer benefit to the next generation.

6.1.3 Early pregnancy

Embryogenesis is largely determined in the first trimester. During this time, the developing embryo is exquisitely sensitive to environmental factors. The role of toxins, infections (such as rubella) and nutritional deficiencies (e.g. in folate, iodine) in organogenesis is well recognized. However, evidence is mounting that more subtle environmental influences operating during early pregnancy may also influence the outcome of pregnancy.

6.1.4 Mid and late gestation

Once the placenta is fully established, fetal development is dependent on the integrity of the maternal-placental unit. Infections such as malaria can interfere with placental function, thereby impairing the delivery of nutrients to the fetus and constraining fetal growth. Fetal growth is also heavily influenced by maternal stress and workload, the mother's metabolic energetics and her general health. In addition, toxins, such as drugs of abuse, ethanol and tobacco, are well recognized as being detrimental to optimal fetal growth. Ascending infection and low-grade inflammation have been associated with an increased risk of premature delivery. Abuse, overwork and poor nutrition are all known to exert a negative influence on late gestational fetal growth and, possibly, increase the risk of a preterm birth.

6.1.5 The peri-partum period

Both maternal and infant outcomes are heavily dependent on the availability and quality of intrapartum care. Pre-delivery triage (which ensures appropriate levels of care) can do much to reduce the risk of death, infection and bleeding for the mother, and the risk of death, or of peri-partum asphyxia and subsequent encephalopathy for the baby.

6.1.6 The neonatal period and beyond

The health of the neonate is greatly influenced by its maturity and size, and also by the quality of intrapartum care, the establishment of breastfeeding and the quality of parental investment in that infant. The importance of breastfeeding, in particular, is well established. At this stage, environmental factors start to influence the quality of cognitive development. All of these factors are dependent on the health of the mother, which requires close surveillance in the first days and weeks after birth in order to detect and treat infection and lactation failure, and to promote and support exclusive and prolonged breastfeeding and a stimulating emotional environment. The importance of the health of the mother-infant dyad, a concept that extends from conception well into childhood, was a recurrent theme throughout the Consultation.

6.1.7 Intergenerational factors

The role of the grandmother in a family unit as a determinant of second generational infant survival is well documented (see section 5.2). This cycle, through which environmental factors in one generation influence in turn the health outcomes of the second generation, is an important reason why long-term outcomes must be considered when evaluating pregnancy outcomes and planning interventions. In this context, other intergenerational factors that operate through family and social structures must also be considered.

Application of a life-cycle based approach can usefully guide the orientation and emphasis of an overall strategy aimed at promoting optimal fetal development. Clearly any strategy that only starts once an established pregnancy has been identified risks missing many key opportunities to implement potentially cost-effective interventions. By the same token, nor can a focus on the later stages of pregnancy and the immediate perinatal period be expected to achieve maximum benefits. It was the considered view of the Consultation that any international effort to optimize fetal development should take account of all seven stages identified above, that is to say, any global strategy for optimizing fetal would have to be context-specific.

6.2 Nutrition as an intervention

When food is scarce, women readily forgo their own nutritional health in favour of providing for their children and spouse. Ensuring national and household food security is therefore an important mechanism for protecting the nutritional status of girls, women and mothers at all stages of the life-cycle across the whole population. Thus, in terms of an overall global strategy for enhancing fetal development, the emphasis for diet-based interventions should be on sustainable approaches which increase the availability of a good quality, well-balanced diet rather than on more specific interventions, for example, supplementation with single micronutrients, macronutrients or energy. Ensuring food security implies providing adequate availability of, and access to, food in sufficient quantity and of adequate quality (i.e. with adequate energy and an appropriate balance of macro- and micronutrients). It is the responsibility of government to ensure food security for all groups in the population.

Available food not only has to provide adequate amounts of nutrients, but must also be microbiologically and toxicologically safe for each individual in the population. The nutrient supply to the population can be improved by a variety of interventions that enhance the quality of foodstuffs at different stages along the food chain; such interventions may include the modification of cultivation techniques, improvements in food processing techniques and the fortification of selected foods. The potential benefits of interventions of this nature are considerable; the fortification of table salt with iodine and the fortification of flour and pasta with folic acid, for instance, have both produced significant positive impact on pregnancy outcomes. These particular examples are aimed at improving the nutrient supply to the whole population, but the possibility of administering a multiple micronutrient supplement during pregnancy (not just iron and folic acid) is currently being investigated in multi-country trials.

7. Knowledge gaps and priorities for future research

Although most countries already collect data on birth weight and other measures of fetal growth on a routine basis, many still need help with collating and using such data more effectively, in particular, to provide broader measures of fetal development (which could then be analysed at the group and population level; see section 3.2) and also to inform practice and to assess the quality and delivery of health care. For

instance, weight gain during pregnancy is monitored extensively as a part of antenatal care in Latin America; properly collated this information could provide a useful perspective on the maternal health and fetal development. In the absence of randomized controlled trials, observational data of this kind could also be used for comparative purposes, both within and among countries. The use of raw data (such as counting births and weighing) to audit programmes and outcomes and to assess the potential utility of the data collection process to public health surveillance systems can ultimately lead to positive effects on neonate survival. For these reasons the Consultation considered that there would be benefit in commissioning a comparative analysis of current practice in data collection and collation and also how these data are used to inform policy and shape the delivery of health care.

The Consultation identified a need to explore in greater detail the value of referencing birth weight to maternal size and to investigate its relevance to the assessment of the situation of individual children. The potential of this approach as a means of identifying a mechanism by which an informative measure of optimal fetal development might be established also needs further investigation. A requirement for better information on the maternal and infant outcomes of adolescent pregnancies, this being a group with special difficulties, was also highlighted.

Historically, policy-makers have tended to concentrate their attention on measurable outcomes or on the short term, largely because when planning services it is important to be able to quantify progress towards defined objectives. The past focus on achieving reductions in mortality is a good case in point. Considerable progress has undoubtedly been made in reducing total population mortality, often reflecting lower mortality among young children. However, achieving equivalent gains in morbidity and mortality in older age groups will increasingly become dependent on finer qualitative improvements during early life. The attainment of longer-term benefits through a focus on a healthy start to life will increasingly be of fundamental importance in all societies and will generate a considerable return on the initial investment and a favourable cost–benefit ratio over time. There is therefore an urgent need for advocacy that places emphasis on the functional benefit to be gained from an improvement in fetal development. In addition to the biological benefits, recognition should be given to the potential for considerable improvements in cognitive development, behaviour, social maladjustment and delinquency. The foundations of these potential

benefits have to be established early in life and, as with other developmental processes, are not fully recoverable if damaged or lost during the first years of life.

The Consultation considered that it would be instructive to use what data are available to estimate population attributable costs for various fetal development outcomes. At the present time, the tools for comparing the costs and benefits of achieving optimal fetal development are inadequate, and although it is possible to model the complexity of inputs and outcomes associated with optimal fetal development, the discount rate that is inevitably used puts prenatal care at a considerable disadvantage in relation to the interventions later in the life course. There is probably a strong case for arguing for a lower or zero discount rate, but this still needs to be demonstrated and fully justified.

Further areas of work identified by the Consultation included the compilation of a compendium of information on approaches to optimizing fetal development, covering the “grey literature” (e.g. programme evaluations and experiences in refugee camps), as well as the published literature. A detailed analysis of how specific health policies have influenced programmes and outcomes related to optimal fetal development was also proposed as a priority area for future research effort. It was also recommended that the knowledge base relating to body composition and optimal fetal development be enhanced, and that the potential to do this using sentinel populations and prospective longitudinal studies on populations be explored, especially if such studies could be carried out in populations in transition, and/or in Diaspora or migrant populations.

Other knowledge gaps that were highlighted are as follows:

- pre-conceptual factors determining fetal development;
- paternal factors determining fetal development;
- cognitive outcomes after interventions in pregnancy and early infancy;
- impact evaluations (including improved tools for evaluating cost-effectiveness) of public health interventions and packages relating to fetal development.

8. Recommendations

There is now substantial consensus that environmental influences (including, but not limited to, maternal nutrition) during early life can have a fundamental impact on human development, with consequences for biological and social function and behaviour throughout the life-course (34 *Bhutta et al., 2005*). The consequences are substantial, both in terms of the health costs and the loss of human capital, and provide ample justification for the formulation of a concerted global strategy to optimize fetal development. The recommended approach to developing such a strategy is one in which people and programmes are brought together with the objective of developing a strategy that takes stock of the complexity of factors that need to be addressed if optimal fetal development is to be secured. Underpinning the strategy, and viewed as an absolute pre-requisite to any other action for optimizing fetal development, is a focus on the continuing need for the provision of basic maternal and child health care according to WHO guidelines (3).

The Consultation made the following specific recommendations regarding strategy development:

- The global strategy itself needs to recognize that physical growth is but one aspect of fetal development, and that the wider complexities of the interactions between structure and function must also be acknowledged and addressed. This implies engagement with multiple partners, and encouragement of their active involvement in achieving the desired objective. These considerations represent a major paradigm shift, and the nature of this change in perspective would need to be adequately communicated.
- Other key features of an overall strategy to optimize fetal development that would need to be highlighted are as follows:
 - the change in focus to one that emphasizes the importance of the mother-infant dyad;
 - a life-course approach to strategy development, with an integrated multidisciplinary basis that encompasses survival, morbidity and fetal development;
 - a focus on fetal development rather than fetal growth;
 - recognition of the fact that the application of current knowledge can improve pregnancy outcomes in all societies.

- In the context of existing information, diffusion of knowledge is critical. The strategy should therefore include a strong political advocacy component, which by building consensus and developing high-profile communications, has the capability to give voice to the voiceless.
- Many of the required components of a strategy for promoting optimal fetal development already exist as single packages. By embedding these components in a broader framework, other approaches and programmes (such as IMCI, Making Pregnancy Safer, Roll Back Malaria and those tackling the problem of HIV/AIDS), can become part of an overall package of measures which collectively work together to secure strategy objectives.
- As the lead agency for standardizing data collection methods and ensuring the quality of training materials, WHO should recognize the need for sustained advocacy of the fundamental importance of optimal fetal development for the health of all societies, and accept appropriate responsibility. Optimal fetal development should be seen as an integral aspect of societal development and the achievement of health for all. It is of critical importance that there is full appreciation of the substantial benefits to be gained by integrating policies and activities which seek to achieve optimal fetal development, in order to gain synergies across a wide range of programmatic activities.
- The Millennium Development Goals (MDGs) offer a timely opportunity for advocating for a strategy to promote optimal fetal development. Advocacy documents which argue for the adoption of multiple packages that ensure optimal fetal development as a means of achieving the health and the poverty reduction goals of the MDGs are urgently needed. In addition, guidelines that set out those elements of pregnancy, childbirth and prenatal care packages that need to become essential components of poverty reduction strategy papers in all countries should be produced. These guidelines should highlight the fact that survival, quality of life and human capital are greatly influenced by sub-optimal development during early life, and that improvements in fetal development will have a major impact on health and development indicators, which ultimately will become self-sustaining.

- A list of interventions – with a description of how each can contribute to achieving optimal fetal development – aimed at policy-makers should also be produced. These information packages would need to be tailored to suit different settings. Regional meetings will be another important part of the process of gaining support and acceptance of the strategy. The involvement of sister UN agencies (e.g. the Food and Agriculture Organization of the United Nations (FAO), the United Nations Children’s Fund (UNICEF) and the United Nations Population Fund (UNFPA)) was seen to be vital to the process of gaining regional support for the strategy. In order to enlist their support, and to have them as active participants from the outset, it was recommended that the views of the relevant UN agencies be sought at a very early stage. To this end, it was proposed that ways in which partner agencies could become actively involved in strategy development should be explored as soon as possible.
- A major effort should be devoted to the monitoring and evaluation of ongoing activities aimed at achieving optimal fetal development. Countries should be encouraged, and if necessary supported, to begin to look at the issue of fetal development. Existing programmes, as well as the information systems that inform such programmes, should be critically reviewed as part of this initiative. This is especially relevant in the case of key strategy components, such as age at first pregnancy, safe motherhood, and quality of perinatal and newborn care. These measures, among others, may well need to be addressed as part of any future national programme of interventions to promote fetal development. Testing the effectiveness of articulated packages of interventions for promoting optimal fetal development remains a key challenge but the experience gained by WHO in evaluating IMCI and safe motherhood programmes provides an excellent basis from which to build.

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**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.

**WHO Technical Consultation towards the Development of a
Strategy for Promoting Optimal Fetal Development**
Geneva, 25–27 November 2003

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

In December 2002, a group of experts met under the auspices of the WHO to discuss the desirability of developing a global strategy to reduce the prevalence of low birth weight (defined as a birth weight below 2500 grams). It became apparent that the development of a strategy that was focused on low birth weight per se alone would not address the central issue of ensuring a healthy start in life and that it would be more appropriate to work towards a strategy aiming to the *optimization of fetal development* in the broadest sense of the term. This theme was explored more fully during a follow-up Consultation held in November 2003, at which participants were requested to review current knowledge about the measurement, causes and consequences of sub-optimal fetal development and to propose next steps in the strategy development process. This report presents the findings of that Consultation.

There can be no doubt that early life events have a critical impact on human development, with consequences for biological and social function and behaviour over the entire life-course. It thus follows that any strategy which promotes a healthy start to life has the potential to improve a plethora of outcomes including infant and child survival, school performance and skills, health in infancy, childhood and adolescence, the health of the next generation of mothers and their fetuses, adult health and productivity. In other words, a strategy to optimize fetal development, if implemented, would not only have immediate health benefits, but also cumulative benefit for personal and social health and development for over many decades to come and as such would be in close accord with the Millennium Development Goals.

In terms of interventions aimed at securing optimal fetal development, the Consultation highlighted the importance of a continued focus on the provision of basic health care and obstetric facilities and also the need for improved coordination in the delivery of health-care services to mother and child. The Consultation considered that the information needed to support the formulation of a holistic strategy for global application already existed, but acknowledged that some raw data still needed to be collected and analysed, and a number of core knowledge gaps had yet to be addressed.

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