The Epidemiology of Adverse Pregnancy Outcomes: An Overview

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ABSTRACT This paper provides an overview of the occurrence, etiology and temporal trends of adverse pregnancy outcomes. Disparities between developed and developing countries are highlighted for maternal mortality, infant mortality, stillbirth and low birth weight. The higher rate of low birth weight in developing countries is primarily due to intrauterine growth restriction rather than preterm birth. Much of the excess intrauterine growth restriction is caused by short maternal stature, low prepregnancy body mass index and low gestational weight gain (due to low energy intake). No important contribution has been established for micronutrient intake, nor have different fetal growth trajectories been demonstrated to reflect the timing of exposure to nutritional or other etiologic factors. Infant mortality has declined substantially over time both in developed and developing countries despite no decline (and even an increase) in low birth weight. Several developed countries have reported a temporal increase in fetal growth in infants born at term, a reduction in stillbirth rates and prevention of neural tube defects. More progress is required, however, in understanding the etiology and prevention of preterm birth. J. Nutr. 133: 1592S–1596S, 2003.

KEY WORDS: • infant mortality • stillbirth • low birth weight • preterm birth • intrauterine growth restriction

In most developed countries, pregnancies are planned, complications are few and outcomes are generally favorable for both mother and infant. Adverse outcomes are far more frequent in the developing world. The most severe adverse outcome of pregnancy is the death of the mother or her offspring. Maternal death has become an extremely rare event in the developed world, with many countries reporting maternal mortality ratios of 5–10 per 100,000 live births. In the least developed countries, the ratios are 100 times higher (1,2). Disparities in infant deaths are not quite as wide but remain substantial, ranging from 4–5 to >100 per 1000 live births (3,4). Wide disparities probably also exist in the rate of late fetal deaths (stillbirths), although fetal deaths in developing countries are grossly underreported (5,6). Even if both the mother and infant survive, pregnancy complications or problems at delivery or during the neonatal period can lead to severe maternal or infant morbidity (7–11).

Despite the recognized importance of mortality and severe morbidity as measures of adverse pregnancy outcome, much of the published research in the area of adverse pregnancy outcomes, especially those outcomes related to maternal nutrition, are based on proxy outcomes for mortality and severe morbidity. The most commonly studied of these proxies have been low birth weight (LBW) 1, including its constituents, preterm birth and intrauterine growth restriction (IUGR) and congenital anomalies.

Low birth weight is defined by the World Health Organization (WHO) as a birth weight <2500 g. Birth weight, however, is determined by two processes: duration of gestation and rate of fetal growth (12). Thus, infants can have a birth weight <2500 g either because they are born early (preterm birth) or are born small for gestational age (SGA), a proxy for IUGR. WHO defines preterm birth as delivery before 37 completed weeks of gestation and SGA as a birth weight below the 10th percentile for gestational age based on the sex-specific reference by Williams et al. (13). Some SGA infants are merely constitutionally small rather than nutritionally growth restricted; conversely, some IUGR infants who would otherwise be constitutionally large do not meet the standard criteria for SGA. Moreover, newborn infants may be growth-restricted or preterm without having LBW (14). For example, the WHO cutoff for SGA for males at 40 wk is 2944 g whereas the median birth weight for males at 35 wk is 2562 g (13).

One of the reasons that LBW continues to be reported and studied by epidemiologists and public health practitioners is that it can be measured with excellent validity and precision. Measuring preterm birth or IUGR requires a valid estimate of gestational age, which is often difficult in developing countries because of late and infrequent access to prenatal care, inadequate medical facilities, and lack of trained personnel to perform ultrasound examinations. A widely used estimate of gestational age in many developing countries is based on maternal age, duration of pregnancy, or length of stop.

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3 Abbreviations used: BMI, body mass index; IUGR, intrauterine growth restriction; LBW, low birth weight; SGA, small for gestational age; WHO, World Health Organization.
the date of the last menstrual period and unavailability of early ultrasound examination.

Despite widespread recognition of the importance of LBW in developing countries, reliable data on its magnitude and distribution remain limited. de Onis et al. (15) recently compiled information on birth outcomes around the world, from which they estimated that 20.5 million LBW infants were born in 1995 and that 16% of all newborns in developing countries were LBW. Table 1 is taken from data reported in the WHO Collaborative Study of maternal anthropometry and pregnancy outcomes (16), the United Nations Children’s Fund’s The State of the World’s Children 2003 (4), and the March of Dimes’ PeriStats (17). In countries where the prevalence of LBW is very high, most LBW infants are growth restricted rather than preterm (15,18). As seen in Table 1, the prevalence of IUGR varies widely among developing countries: 30–55% of infants born in South Central Asia versus 15–25% in Africa and 10–20% in Latin America. Caution is again advised in interpreting the values in Table 1 because of the absence of universal birth registration and the poor gestational age data in many developing countries.

The etiologic determinants of preterm birth and IUGR differ, so that lumping them together as LBW can hinder progress in developing preventive interventions (12,19). Table 2 lists the most important etiologic determinants of preterm birth and IUGR in developing countries (14). For IUGR the most important determinants are low energy intake and consequent low gestational weight gain, low prepregnancy body mass index (BMI), short stature, primiparity, pregnancy-induced hypertension and, where prevalent, cigarette smoking and (for primiparae) malaria. Important causes of preterm delivery include genital tract infection, multiple birth, pregnancy-induced hypertension, low prepregnancy BMI, incompetent cervix, history of prior preterm birth, heavy work and (where prevalent) cigarette smoking. A short interval (<6 mo) between pregnancies is often cited as a determinant of preterm birth or IUGR (20,21), but few studies have controlled for the outcome of the previous pregnancy and the tendency of preterm birth or IUGR to repeat in subsequent pregnancies (22,23). Moreover, intervals <6 mo are infrequent in developing countries where prolonged and exclusive breast-feeding are prevalent.

IUGR and preterm birth also have important differences with respect to prognosis. Preterm infants are at increased risk of death (10,24,25); short- and long-term pulmonary (10), ophthalmologic (11) and neurologic morbidity; and delayed psychomotor development (26,27). Severe growth-restricted fetuses are at increased risk of stillbirth (28–31) and those born alive have an increased risk of neonatal death and of significant short-term morbidity from hypoglycemia, hypocalcemia and polycythemia (31). Over the longer term, IUGR infants tend to have small but permanent deficits in growth (32) and neurocognitive development (33–37). Epidemiologic studies by Barker (38), Leon (39) and others suggest that such infants may be at an increased risk of type-2 diabetes, hypertension and coronary artery disease when they reach middle age many decades later.

### Methodological issues

**Fetal growth trajectories.** Various body proportionality indices have been used to relate different dimensions of fetal growth, particularly among growth-restricted infants. The most commonly used of these is Rohrer’s ponderal index, a measure of birth weight relative to birth length, which is defined as 100 times the birth weight in grams divided by the birth length in centimeters cubed. The ponderal index is often then used to subdivide IUGR infants into those who are proportionate (also called symmetric or stunted) and disproportionate (asymmetric or wasted) (40,41). Many investigators have assumed that differences in proportionality at birth reflect differences in timing of intrauterine growth restriction on the basis of highly diagrammatic fetal growth velocity curves published by Tanner (42), which suggested deceleration in length growth in the second trimester. In fact, studies based on serial ultrasound measurements (43) or prostaglandin-induced pregnancy ter-

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### TABLE 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Low birth weight (% of live births)</th>
<th>Intrauterine growth restriction (% of live births)</th>
<th>Preterm (% of live births)</th>
<th>Infant mortality (per 1000 live births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>6.3</td>
<td>9.7</td>
<td>7.2</td>
<td>16</td>
</tr>
<tr>
<td>China</td>
<td>4.2</td>
<td>9.4</td>
<td>7.5</td>
<td>31</td>
</tr>
<tr>
<td>Colombia</td>
<td>16.1</td>
<td>17.8</td>
<td>15.7</td>
<td>19</td>
</tr>
<tr>
<td>Cuba</td>
<td>8.1</td>
<td>14.7</td>
<td>7.2</td>
<td>7</td>
</tr>
<tr>
<td>Gambia</td>
<td>12.1</td>
<td>13.5</td>
<td>13.5</td>
<td>91</td>
</tr>
<tr>
<td>Guatemala</td>
<td>12.5</td>
<td>25.3</td>
<td>15.8</td>
<td>43</td>
</tr>
<tr>
<td>India (Pune)</td>
<td>28.2</td>
<td>54.2</td>
<td>9.7</td>
<td>67</td>
</tr>
<tr>
<td>Indonesia</td>
<td>10.5</td>
<td>19.8</td>
<td>18.5</td>
<td>33</td>
</tr>
<tr>
<td>Ireland</td>
<td>5.6</td>
<td>6.9</td>
<td>6.2</td>
<td>6</td>
</tr>
<tr>
<td>Malawi</td>
<td>11.6</td>
<td>26.1</td>
<td>8.2</td>
<td>114</td>
</tr>
<tr>
<td>Myanmar</td>
<td>17.8</td>
<td>30.4</td>
<td>24.6</td>
<td>77</td>
</tr>
<tr>
<td>Nepal (Rural)</td>
<td>14.3</td>
<td>36.3</td>
<td>15.8</td>
<td>66</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>18.4</td>
<td>34.0</td>
<td>14.0</td>
<td>17</td>
</tr>
<tr>
<td>Thailand</td>
<td>9.6</td>
<td>17.0</td>
<td>21.3</td>
<td>24</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>6.2</td>
<td>12.3</td>
<td>4.6</td>
<td>6</td>
</tr>
<tr>
<td>U.S./CDC</td>
<td>10.6</td>
<td>11.2</td>
<td>16.6</td>
<td>14</td>
</tr>
<tr>
<td>U.S./CDC (Hispanic)</td>
<td>4.8</td>
<td>5.8</td>
<td>10.2</td>
<td>6</td>
</tr>
<tr>
<td>U.S./CDC (White)</td>
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<td>6.9</td>
<td>9.3</td>
<td>6</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5.2</td>
<td>18.2</td>
<td>13.6</td>
<td>30</td>
</tr>
</tbody>
</table>

1 Adapted from reference 16.
2 Adapted from references 4 & 7.
3 U.S. Centers for Disease Control and Prevention.

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### TABLE 2

<table>
<thead>
<tr>
<th>Preterm birth</th>
<th>Intrauterine growth restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital tract infection</td>
<td>Low energy intake, low gestational weight gain</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>Low prepregnancy body mass index</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>Short stature</td>
</tr>
<tr>
<td>Low prepregnancy body mass index</td>
<td>Malaria3</td>
</tr>
<tr>
<td>Incompetent cervix</td>
<td>Cigarette smoking4</td>
</tr>
<tr>
<td>Prior preterm birth</td>
<td>Primiparity</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>Pregnancy-induced hypertension</td>
</tr>
<tr>
<td>Heavy work</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Cigarette smoking4</td>
<td>Other genetic factors</td>
</tr>
</tbody>
</table>

1 Listed in decreasing order of importance.
2 Adapted from reference 14.
3 For primiparae in malaria-endemic areas.
4 Where maternal smoking during pregnancy is prevalent (10–20%).
minations (44–46) clearly demonstrate that crown-to-heel length, biparietal diameter and head circumference increase linearly throughout the second trimester. Moreover, proportionality among IUGR infants is strongly confounded by the severity of the growth restriction (i.e., disproportionate IUGR infants tend to be more severely growth restricted than their proportionate counterparts) (47,48).

Stillbirth. A number of important methodological issues arise with respect to stillbirth. As previously mentioned, stillbirths are grossly underreported in developing countries (5,6). However, even in developed countries, wide differences exist concerning the gestational age at which stillbirth registration is legally required and in the classification of stillbirths versus live births despite universal adoption of the WHO International Classification of Diseases definition of a live birth (49).

Total stillbirth rates are generally reported as the number of stillbirths beyond a certain gestational age or birth weight (typically 20 or 22 wk and 500 g, respectively) divided by the number of total births (live births plus stillbirths) that meet the same gestational age or birth weight criteria. Many epidemiologists and public health practitioners, however, have stratified the overall stillbirth rate by gestational age or birth weight. This is clearly inappropriate because the denominator (the number of stillbirths and live births at a given gestational age or birth weight) is only a subgroup of all fetuses at risk, and the resulting proportion (rate) is conditional on birth at that gestational age or birth weight. This type of inappropriate measure of stillbirth risk leads to the completely mistaken notion that stillbirth risk decreases as gestation advances. In fact, when the risk of stillbirth is expressed appropriately as a proportion of all ongoing pregnancies, the risk rises as term approaches and is highest in the postterm period (50,51).

Measurement issues. Our ability to measure micronutrient intake is a problem because of imprecision in the measurement of dietary intake and variation in intake over time, particularly as gestation advances (52,53). Micronutrient status is also affected by variations in metabolism and excretion, and blood levels of many micronutrients may vary as a result of physiological dilution caused by the plasma volume expansion that is a normal physiological manifestation of pregnancy (54). Blood levels are also subject to other environmental and physiological influences. For example, zinc concentrations fall (55) and ferritin concentrations rise (56) in response to infection.

Causal inference. In isolating the effect of one or more micronutrients on pregnancy outcome, an important methodological issue to consider is the strong correlation among micronutrients and between micronutrients and macronutrients. This creates a large potential for confounding by other micronutrients and by overall energy intake and leads to major inferential problems for causality (12).

Confounding is also a major issue with respect to socioeconomic status and the above-noted hemodynamic changes. Women with low micro- and macronutrient intakes are often those of lower education and income, which are associated with many adverse behavioral and psychosocial factors that can cause adverse pregnancy outcomes, such as cigarette smoking, drug use, sexual practices and stress (57). Plasma volume expansion can lower micronutrient levels and thus negatively confound the true effects of micronutrient deficiency (54). These issues of confounding underline the importance of randomized trials of individual micronutrients or combinations of micronutrients in establishing causal effects and in evaluating interventions to prevent adverse pregnancy outcomes.

Temporal trends

Temporal trends in adverse pregnancy outcomes have provided a mixture of both good news and bad. The good news is that infant mortality has fallen in many parts of the world. It is essential to point out that this decrease in infant mortality has occurred on a background of little or no success in preventing LBW. Rather, infant mortality has been reduced at all birth weights, including infants of normal birth weight (58–60). In some developing countries with reliable national or regional birth registration, preterm birth appears to be on the rise (61,62), as has been reported from most developed countries (63–65). The temporal increase in preterm birth is primarily due to an increase in obstetric intervention, which is often motivated by a desire to reduce the risk of stillbirth and of maternal mortality and severe morbidity (66). In developed countries a rise in multiple births (attributable to hormonal treatments and assisted reproduction technologies for infertility) has also been an important cause of the trend toward increasing preterm birth (67).

Some developed countries, including Canada, the United States and Norway have reported a temporal increase in fetal growth and particularly in the size of infants born at term (68–70). No consistent increase has been seen in the size of preterm infants.

Several developed countries have reported a fall in stillbirth rates (63). Neural tube defects have recently been falling in developed countries, particularly those that have promoted preconceptional folic acid supplementation and (probably even more importantly) food fortification with folic acid (71,72). Data from China suggest that folic acid supplementation is a feasible public health objective in developing countries as well (73). A recent report from Canada has shown, for the first time, that prevention and termination of pregnancies with congenital anomalies has had a perceptible effect on overall infant mortality (74). The prospects are excellent that this trend will continue in the future and it is hoped that it will spread to developing countries as well.

Despite this evidence of progress, important gaps remain in our knowledge base:

- The above-noted improvements in pregnancy outcome have not included reductions in preterm birth and many countries have reported an increase (61–63,65). Clearly, much more needs to be known about the etiology of preterm labor and preterm prelabor rupture of membranes.
- The etiology of preterm birth may have rather little to do with micro- or macronutrient status or even with maternal nutrition in a general sense. Given the limited success of perinatal epidemiologic research in understanding the etiology of preterm birth, we may first have to learn more about the molecular mechanisms underlying preterm labor and membrane rupture.
- Improved epidemiologic studies will require the use of biological markers, investigation of gene-environment interactions, a better understanding of how social and psychological determinants contribute to the pathophysiology of preterm delivery, and developing and testing of interventions to prevent and treat genital tract colonization and inflammation.

LITERATURE CITED


