Table 10  Prevalence of night blindness and number of individuals affected among preschool-age children and pregnant women in populations of countries at risk of vitamin A deficiency 1995–2005, globally and by WHO region

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Preschool-age children</th>
<th>Pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td># affected (millions)</td>
</tr>
<tr>
<td>Africa</td>
<td>2.0 (0.8-3.2)</td>
<td>2.55 (0.99-4.11)</td>
</tr>
<tr>
<td>Americas</td>
<td>0.6 (0.0-1.3)</td>
<td>0.36 (0.00-0.75)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>0.5 (0.0-2.0)</td>
<td>1.01 (0.00-3.75)</td>
</tr>
<tr>
<td>Europe</td>
<td>0.8 (0.1-1.5)</td>
<td>0.24 (0.04-0.44)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>1.2 (0.6-1.7)</td>
<td>0.77 (0.41-1.12)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>0.2 (0.0-0.4)</td>
<td>0.26 (0.02-0.50)</td>
</tr>
<tr>
<td>Global</td>
<td>0.9 (0.3-1.5)</td>
<td>5.17 (1.97-8.38)</td>
</tr>
</tbody>
</table>
**Increased risks associated with maternal micronutrient deficiencies**

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Magnesium</th>
<th>Vitamin D deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>pregnancy-induced hypertensive disorders</td>
<td>pregnancy-induced hypertensive disorders</td>
<td>Poor fetal growth and skeletal mineralization</td>
</tr>
<tr>
<td>preterm delivery</td>
<td></td>
<td>Low concentration in breast milk</td>
</tr>
<tr>
<td>pre-eclampsia</td>
<td></td>
<td>Risk of long-term outcomes (type 1 diabetes, multiple sclerosis, &amp; other chronic diseases)</td>
</tr>
</tbody>
</table>

Khor GL 2011
Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon Study

Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured at 28–32 week gestation in 568 women.

Anthropometric variables, blood pressure, glucose, insulin and fasting lipid concentrations were measured in the offsprings at 5 and 9.5 y of age.

At ages 5 and 9.5 years, children born to vitamin D deficient mothers had significantly smaller arm-muscle area in comparison with children born to mothers without deficiency.

At 9.5 years, children of vitamin D deficient mothers had significantly higher fasting insulin resistance than did children of non-deficient women.

Khor GL 2011
Intergenerational effects of maternal micronutrient malnutrition
Maternal nutrition during pregnancy may predispose child to a greater risk of chronic disease in later life

Since Barker and his associates from the University of Southampton forwarded the fetal origins of adult chronic disease in the early 1980s, evidence has emerged implicating maternal hormonal and nutrient environment in systematically affecting the developing fetus, leading to increased susceptibility to metabolic, neurodevelopmental, and psychiatric diseases in adulthood.

Vitamin B$_{12}$ and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study

- The Pune Study (Maharashtra, India) began in ~1994 with over 2600 married women. Over the years, 797 women who became pregnant were examined for their nutritional status, biochemical parameters and fetal growth.

- A total of 653 children were followed up with repeat anthropometry every 6 months.

- The offsprings of mothers with a combination of high folate and low vitamin B$_{12}$ concentrations were the most insulin resistant by age 6 years.
The results raise the important possibility that high folate intakes in vitamin B$_{12}$-deficient mothers could increase the risk of type 2 diabetes in the offspring.

Fig. 2 Insulin resistance (HOMA-R) in the children at 6 years in relation to maternal vitamin B$_{12}$ (18 weeks) and erythrocyte folate (28 weeks)

Khor GL 2011
Maternal undernutrition, stress

- Reduced fetal growth
- Low birth weight
  compensated by early catch-up growth

- Increased prevalence of metabolic diseases, such as obesity and diabetes, as well as neurodevelopmental disorders.

Maternal obesity, diabetes

- Increased fetal growth

- Increased prevalence of insulin resistance, hypertension in offspring.

Khor GL 2011
Impact of maternal obesity on offspring obesity and cardiometabolic disease risk

“It is now recognised that maternal obesity has long-term adverse outcomes for the health of her offspring in later life”.

“Of particular concern is the increased risk of obesity and metabolic sequelae in the offspring of obese mothers, which has the potential to result in an ‘intergenerational cycle’ affecting obesity and cardiovascular disease risk across a number of generations”.

Khor GL 2011
The recurring nightmare: cycles of disease with a poor start to life (Hanson & Gluckman, 2005)

- Women malnourished
- Low pregnancy weight gain
- Very poor postnatal environment
  - Stunting
- Maternal morbidity

Suboptimal fetal development

- Obesity
- Insulin resistance
- Enriched postnatal environment

- Premature death and morbidity
- Maternal morbidity

Gestational diabetes

- Large babies

Obese mothers

- Large babies

Khor GL 2011
Implications of micronutrient deficiency in fetal programming

- The actual mechanisms linking an adverse intrauterine environment to adult disease are still under intense investigation.

- Recent hypotheses have proposed mechanisms that involve the placenta playing an active role.

Hence the traditional view of the placenta as a passive site of transport of maternal nutrients, growth factors, and hormones is being challenged
The placenta responds to and modulates perturbations in the maternal environment

1. Structural alterations

e.g. in the IUGR placenta, the villi are poorly branched and capillarized, and the exchange placenta barrier is thickened.

(Jansson & Powell, 2007; Broad & Kevin, 2011)
Structure of the term human placenta

Figure 1  Structure of the term human placenta
1. Syncytiotrophoblast; 2. fetal capillary with erythrocytes; 3. MVM; 4. BM; 5. umbilical vein; 6. umbilical arteries; 7. chorion plate; 8. decidua; 9. myometrium; 10. intervillous space with maternal blood; 11. veins; 12. spiral arteries; 13. villus tree; 14. syncytiotrophoblast cell nuclei; 15. diffusion distance between maternal and fetal blood. The insert to the right is a magnification of the placental barrier. This Figure was reproduced from [136] with permission.

(Jansson & Powell, 2007)
Khor GL 2011
Thickening of the placental exchange barrier, a primary cause of fetal hypoxia in IUGR, and the increased placental vascular resistance in IUGR may represent alterations in placental structure that are directly involved in the fetal programming of cardiovascular disease.

As proposed by Thornburg and Louey (2005), this subjects the IUGR fetal heart to an increased pressure work load, which is suggested to result in an adaptation that may be advantageous in the short term perspective, but could contribute to cardiovascular disease postnatally.
2. Decreased activity of key barrier enzyme on the placenta:

Abnormally high levels of maternal corticosteroids result in IUGR, elevated blood pressure, insulin resistance and altered fat metabolism in later life.

Placental 11β-HSD-2 (hydroxysteroid dehydrogenase forms a functional barrier restricting the free transfer of cortisol between the maternal and fetal compartments by converting cortisol into its much less active 11-keto form, cortisone.

Hence decreased 11β-HSD activity will result in dysfunction in the placental glucocorticoid barrier and expose fetus to excess corticosteroids, thus constituting a direct link between altered placental function and fetal programming.

Regulate placental nutrient transporters

Maternal hormones: insulin, leptin, IGF-1

Fe/Zn deficiency reduces IGF-1 activity

Alterations in placental transporter activity

Fetal programming

Fetal growth

Nutrient supply

Placental mTOR

The mammalian Target of Rapamycin (mTOR) is an important nutrient-sensing protein kinase that regulates numerous cellular processes, in response to nutrient availability.

Figure 2  Placenta as a nutrient sensor: a hypothesis


Khor GL 2011
The “placenta as a nutrient sensor” hypothesis (Janssen & Powell, 2007).

The placenta regulates the amount of nutrients for fetal growth, which is compatible with the availability of nutrients that can be provided by the maternal supply line.

In the case of maternal malnutrition, it is sensed by the placenta and, as a consequence, some key placental transporters are down-regulated in order to decrease fetal growth, resulting in IUGR.

Similarly, hyperglycaemia early in pregnancy may convey a ‘good nutrition’ signal to the placenta, resulting in up-regulation of glucose and amino acid transporters.

Khor GL 2011
The placenta responds to and modulates perturbations in the maternal environment

3. Epigenetic regulations

Epigenetic modification refers to heritable changes in gene expression that are not mediated by alterations in DNA sequence.

Epigenetic mechanisms include methylation, which is dependent on availability of methyl donors such as folate, B_{12} and choline.

Studies indicate that epigenetic regulation of fetal genes represents an important mechanism mediating fetal programming.

These areas of research will attract much interest in the near future.

(Jansson & Powell, 2007; Broad & Kevin, 2011)
Conceptual framework for how maternal diet and micronutrient status may affect the development of chronic disease in the offspring.

Maternal micronutrient deficiency

Hormonal adaptation
*Fe, Zn, Ca*
Increased stress hormones
Decreased somatotrophic Hormones (IGF, insulin)

Epigenetic gene regulation
*Folate, vitamin B$_{12}$*

Restricted fetal growth and development


Khor GL 2011

Khor GL 2011