**Maternal phenylketonuria**

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Abstract

Maternal phenylketonuria (PKU) during pregnancy leads to a risk of spontaneous abortion or embryopathy. The severity of embryopathies depends on the level of maternal phenylalaninemia and may associate malformations including cardiopathy (usually conotruncal), corpus callosus agenesis, neuronal migration disorders, facial dysmorphism and more rarely cleft palate, tracheo-esophageal abnormalities... but especially fetal development disorders, including microcephaly, intrauterine growth retardation, and subsequent mental retardation. This embryopathy can be prevented by a strict low-phenylalanine diet started before conception and maintained throughout pregnancy. Girls with phenylalanine hydroxylase (PAH) deficiency, must be fully informed, so as in to program pregnancies, when the time comes, and control the phenylalanine level before conception. Maternal PKU may be suggested in fetuses or children whose mothers were born before the systematic screening of newborns for PKU or in a country were there is no screening at all.

Keywords

Phenylketonuria, embryopathy, mental retardation, congenital heart disease, microcephaly, phenylalanine hydroxylase

**Disease name and synonyms**

- Maternal hyperphenylalaninemia
- Maternal phenylketonuria
- Maternal phenylketonuria syndrome
- Maternal PKU

**Diagnostic criteria/definition**

Elevated maternal phenylalanine levels during pregnancy are teratogenic and may result in growth retardation, significant psychomotor handicaps and birth defects in the offspring of women whose plasma phenylalanine levels are abnormally high. For women whose phenylketonuria (PKU) was known before pregnancy, the diagnosis of maternal PKU syndrome is based on the ultrasound recordings measuring fetal growth parameters, the examination of the neonate with measurement of birth and growth parameters, searching for compatible malformations, and the follow-up of the child regarding his head circumference.
growth and cognitive milestones. For women not known to have PKU, the diagnosis can be made only if the physician is highly sensitized to such a possibility and indeed thinks of it, measuring the mother’s plasma phenylalanine level.

**Differential diagnosis**
Maternal PKU syndrome resembles several embryopathies, in particular teratogenic embryopathies, such as fetal alcohol syndrome and embryopathies caused by antiepileptic drugs. Differential diagnoses are easy to exclude because maternal phenylalanine levels are normal in all other situations.

**Prevalence**
Theoretically, the prevalence of maternal PKU syndrome should be the same as the prevalence of phenylalanine hydroxylase (PAH) deficiencies itself, i.e. 1/15000 live births on the average (considering the mean reproductive rate per couple to be 2, and since 1 PKU patient out of 2 is female). Fortunately, the actual prevalence is lower than that, since untreated PKU women are mentally retarded and consequently have no or few offspring, and since the majority of treated PKU women are nowadays informed and carefully managed during their pregnancies.

**Clinical description**
The gravity of maternal PKU syndrome is reflected by the maternal plasma concentration; over 20 mg/dL, the risk is major. In 1980, Lenke and Levy published the first exhaustive description of the syndrome, in untreated women. For a plasma concentration over 20 mg/dL during pregnancy, the frequency of each feature was the following:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Mental retardation</td>
<td>92%</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>73%</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>12%</td>
</tr>
<tr>
<td>Birth weight &lt; 2500 g</td>
<td>40%</td>
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</tbody>
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The exact frequencies of the other features are less precise: facial dysmorphism (frequent), corpus callosum agenesis (frequent), tracheoesophageal malformations and cleft palate (rare, 1-5%).

Clinical descriptions have now been reported for groups of women who were (or tried to be) on a low phenylalanine diet during pregnancy. Therefore, the results are expressed according to the quality of the biological control (mean plasma phenylalanine level during a given period of time), during a specific period (before conception, by the first, second or third trimester of gestation).

According to the latest publications by the US Maternal PKU (MPKU) collaborative study, when the maternal phenylalanine level is below 15 mg/dL by 8 weeks of gestation, the risk of congenital heart disease (CHD) is similar to that of the control population. Nevertheless, among the 31 children with CHD out of 413 live births, 7 had been exposed to 10 -15 mg/dL of phenylalanine during the first 8 weeks of gestation. Mean phenylalanine level during weeks 4 to 8 of gestation was the strongest predictor of offspring with CHD. Children with CHD had a 3-fold risk of also having microcephaly. Facial dysmorphism, small head circumference, low birth weight and lower long-term IQ may be observed for children who were exposed to over 6 mg/dL phenylalanine.

The intellectual outcome of the children enrolled in the US MPKU collaborative study depends on how long post-conception the phenylalanine level was maintained below 10 mg/dL. Bayler scores at 2 years of age, McCarty General Cognitive Index at 4/5 years, and WISC-r full scale IQ after 6 years give the same pattern of results. The intellectual levels of the children born to women either with non-PKU hyperphenylalaninemia (without treatment during pregnancy) or with PKU but controlled before conception, are similar and good; those whose mothers controlled their phenylalanine level before 10 weeks of gestation had IQs within the normal range, but about 10 points below the preceding group. Children whose mothers controlled their phenylalanine level between weeks 10 and 20 of gestation, and after 20 weeks of gestation had lower IQs, around 85 and 75, respectively.

The lower limit of the phenylalanine level to eliminate the risk of maternal PKU is not easy to pinpoint, but recommendations advise women to keep their phenylalanine levels as close as possible to the normal, i.e. between 2 and 5 mg/dL. There is a nutritional risk for the pregnant woman to keep her phenylalanine level below that threshold.

**Management**
Maternal PKU syndrome has no curative treatment, in particular no diet, except if the child has a PAH deficiency. CHD or other malformations may require surgical intervention, and mental retardation needs non-specific rehabilitation management.

The main treatment of maternal PKU syndrome is preventive by controlling the plasma phenylalanine levels of the mothers throughout pregnancy. The diagnosis of maternal PKU syndrome may lead to the diagnosis of hyperphenylalaninemia in the mother, and preventive measures have to be taken before a subsequent pregnancy. In screened and treated
PKU women, prevention is achieved good dissemination of information, which must begin during childhood, followed during visits with the adolescent herself, in order to prevent unplanned pregnancies and explain the principles of the low-phenylalanine diet that must be started before conception.

**Etiology**
Maternal PKU syndrome etiopathogenesis is not perfectly understood. During the early stages of embryogenesis, circulating hyperphenylalaninemia has a deleterious effect on neural crest cell migration, thereby explaining facial malformations, conotruncal defects and tracheo-esophageal anomalies. During fetogenesis, circulating hyperphenylalaninemia has deleterious effects on neuronal multiplication and myelogenesis that persist after birth.

**Genetic counseling**
Maternal PKU syndrome is an embryopathy secondary to a maternal genetic disease. Children born to women with maternal PKU syndrome are at least heterozygous. Their status regarding PAH deficiency depends on the father's status. If the father is homozygous for a normal PAH gene, the child will be heterozygous for PKU. If the father is heterozygous for PAH defect, the child will have 50% risk of having PKU. If the father is PKU himself, the child will surely be PKU.

**Antenatal diagnosis**
Maternal PKU syndrome may be suggested during prenatal life, when ultrasound recordings show an embryo with growth retardation, microcephaly, CHD, or other compatible anomalies. The diagnosis is confirmed by measurement of the maternal plasma phenylalanine level. Taking into account the maternal phenylalanine level, the term of the gestation, the ultrasound data, and parents' informed opinion, the specific diet can be initiated urgently or the pregnancy can be terminated.

**References**