Maternal phenylketonuria and hyperphenylalaninemia in pregnancy: pregnancy complications and neonatal sequelae in untreated and treated pregnancies1–3

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ABSTRACT
Background: Untreated maternal phenylketonuria or hyperphenylalaninemia may result in nonphenylketonuric offspring with neonatal sequelae, especially intellectual disability, microcephaly, and congenital heart disease (CHD). Dietary treatment to control phenylalanine concentrations can prevent these sequelae.

Objective: We aimed to present an overview of reported pregnancy complications and neonatal sequelae of maternal phenylketonuria or hyperphenylalaninemia in untreated and treated pregnancies.

Design: A MEDLINE and EMBASE search was conducted for case reports and case series that assessed maternal phenylketonuria or hyperphenylalaninemia during pregnancy. Pregnancy complications (spontaneous abortion, intrauterine-fetal-death, and perterm delivery) and neonatal sequelae (small for gestational age (SGA), microcephaly, CHD, intellectual or developmental disabilities (IDDs), and facial dysmorphism (FD)) were analyzed. Fifteen unpublished pregnancies from our clinic were added.

Results: We retrieved 196 pregnancies, of which 126 pregnancies were untreated and 70 pregnancies were treated. The occurrence of pregnancy complications was not significantly different between untreated and treated pregnancies. Except for SGA, all neonatal sequelae were more frequent in untreated pregnancies. Moreover, the occurrence of SGA, microcephaly, and IDDs was significantly related to the mean phenylalanine concentration in each trimester, whereas the occurrence of FD was related only to the first trimester.

Conclusions: We present the largest cohort of untreated pregnant women with phenylketonuria or hyperphenylalaninemia since 1980. The results follow the general pattern reported by other researchers. We underline that the treatment of pregnant women with phenylketonuria or hyperphenylalaninemia is of great importance to prevent neonatal sequelae. We strongly recommend starting treatment before conception because we showed the deleterious effect of an increased mean first-trimester phenylalanine concentration on FD. Am J Clin Nutr 2012;95:374–82.

INTRODUCTION
Phenylketonuria is an inborn error of metabolism. The prevalence in the Netherlands is 1:18,000 (1). Phenylketonuria is due to a defect in the hepatic enzyme phenylalanine hydroxylase, which converts amino acid phenylalanine into tyrosine. If undiscovered and, therefore, untreated, phenylketonuria may lead to intellectual disability and neurologic disorders (2). Hyperphenylalaninemia is classified by the serum phenylalanine concentration >1200 μmol/L (classical phenylketonuria), between 600 and 1200 μmol/L (mild phenylketonuria), or <600 μmol/L (hyperphenylalaninemia) (3).

Metabolic control of phenylketonuria can be achieved by a strict diet with minimal phenylalanine intake to decrease the serum phenylalanine concentration in combination with tyrosine-enriched supplements (1, 4, 5).

Because routinely postnatal screening on phenylketonuria was introduced in the Netherlands in 1974, more cases of this disorder have been discovered and treated (2). Since then, intellectual disability has been prevented in a substantial number of patients. Consequently, an increasing number of women diagnosed with phenylketonuria or hyperphenylalaninemia reach the reproductive age functioning as normal intellectual and social persons. However, because only minor, unwanted effects of elevated phenylalanine concentrations persist after adolescence, many women do not continue their diet.

Untreated maternal phenylketonuria or hyperphenylalaninemia during pregnancy may lead to maternal phenylketonuria syndrome in the neonate. This syndrome consists of low birth weight, microcephaly, CHD, IDDs, and FD. For this reason, an unambiguous policy to prevent maternal phenylketonuria syndrome is necessary. In this respect, women with a desire to become pregnant are advised to use a strict diet that starts before conception to prevent teratogenic effects in the fetus (6–10). During pregnancy, phenylalanine tolerance improves to some extent because of increased fetal phenylalanine-hydroxylase activity. Consequently, the phenylalanine concentration decreases in the
second trimester, and the intake of proteins can be mildly extended.

The aim of this review was to present an overview of the reported pregnancy complications (eg, spontaneous abortion, IUFD, and preterm delivery) and neonatal sequelae (eg, SGA, microcephaly, CHD, IDDs, and FD) in untreated compared with treated women with maternal phenylketonuria or hyperphenylalaninemia. Because previous studies mainly reported on treated women, we aimed to obtain a large, untreated sample to compare complications and outcomes between untreated and treated pregnancies.

With a review of all reported cases between January 1980 and October 2009, including 15 unpublished cases from our clinic, the search resulted in the largest cohort of untreated pregnancies described since 1980.

METHODS

Data sources and methods of study selection

We reviewed MEDLINE (http://www.ncbi.nlm.nih.gov/) and EMBASE (http://www.embase.com) databases by using the search terms “maternal phenylketonuria” and “phenylketonuria” AND “pregnancy.” The following search strategies were used: PubMed: “maternal phenylketonuria (MeSH)” and “pregnancy (MeSH);” and EMBASE: “phenylalaninemia” and “maternal phenylketonuria.” Case reports and case series from January 1980 to October 2009 that described either untreated or treated pregnancies and were written in English or Dutch were eligible. References from retrieved reports were also screened for eligibility.

In reports describing treated pregnancies, the maternal phenylalanine concentration before conception and a mean concentration per trimester had to be reported. These phenylalanine concentrations were obtained from graphics or text. In cases where phenylalanine concentrations were described as a range, the mean of the summed minimum and maximum of this range was used as the mean phenylalanine concentration in that trimester. The mean phenylalanine concentration per trimester is referred to as the phenylalanine concentration per trimester.

In the untreated group, at least one maternal phenylalanine concentration before or during pregnancy had to be described. If more than one phenylalanine concentration or a range of concentrations were available, the mean was used as the untreated phenylalanine concentration. The untreated phenylalanine concentration was used as the phenylalanine concentration per trimester.

If available, the pregnancy complications spontaneous abortion, IUFD, and preterm delivery were noted. At least one of the neonatal sequelae SGA, microcephaly, CHD, IDDs, and FD had to be mentioned in the text.

Studies that provided ambiguous or insufficient data on patient characteristics, treatment, pregnancy complications, or neonatal sequelae were excluded. By this means, 39 articles fulfilled the inclusion criteria, which described a total of 181 pregnancies in 84 mothers (Table 1). Furthermore, we added unpublished data of 15 pregnancies (1995–2009) from our own clinic. Data of the untreated group were compared with data of the treated group, and pregnancy complications and neonatal sequelae were related to phenylalanine concentration per trimester.

SGA was defined as birth weight <2500 g at term or a birth weight below the 10th percentile. Microcephaly was defined as a head circumference ≤32 cm, below the 10th percentile, or below –2 SDs. IDD refers to this specific textual description or was defined as an IQ or DQ below 80. FD refers to this specific textual description or to facial anomalies of the nose, forehead, mandible, palate, or eyes. Spontaneous abortion was defined as spontaneous pregnancy loss in the first trimester. IUFD was defined as pregnancy loss after the first trimester. Preterm delivery refers to a delivery before 37 wk of gestation. A molar pregnancy refers to a benign form of gestational trophoblastic disease and results of an aberrant fertilization event that lead to proliferative trophoblastic tissue. The initial management of molar pregnancy is evacuation of the uterine contents by suction curettage.

Statistical analyses

Data were analyzed with SPSS 17 (SPSS Inc). The normality of data was determined by using the Shapiro-Wilk’s test and visual assessment. Categorical data (adhesions scores) are presented as numbers with percentages, and numerical data are presented as means ± SEs of the mean (normally distributed) or medians with IQRs (not normally distributed). We investigated the occurrence of pregnancy complications and neonatal sequelae in relation to the phenylalanine concentration per trimester. Many women had more than one pregnancy in this study. Therefore, we used generalized estimating equations (with an exchangeable correlation matrix for the subsequent pregnancies) for the analysis of pregnancy complications and neonatal sequelae to allow for repeated observations (44). For the dichotomous outcomes in the generalized estimating equation analyses, a logit link function was used. The phenylalanine concentrations between the treated and untreated group during all trimesters were compared by using mixed-model ANOVA. In all analyses, phenylalanine concentrations were transformed logistically to get normal-distribution approximations. Significance was defined as P < 0.05. Subjects with missing data were excluded from those specific analysis.

Ethics

The medical ethical committee waived the need for informed consent because of the retrospective and anonymous character of this study.

Additional case series

In our analyses, we included data of 7 patients [6 patients were diagnosed with hyperphenylalaninemia and 1 patient was diagnosed with classic phenylketonuria (patient F)] who were treated and followed in our clinic during their pregnancies. One patient (patient A) was diagnosed with an intellectual disability that was not explained by phenylalanine serum concentrations in childhood. These 7 patients had 15 pregnancies; in 7 pregnancies, dietary treatment was introduced before conception. Consistent
with our local protocol, patients visited the metabolic outpatient clinic on a monthly basis and the dietitian at least every other week. The prescribed diet consisted of a protein-restricted intake with supplementation of amino acids, vitamins, and tyrosine. The target range of phenylalanine was 100–240\,\mu\text{mol}/L. Diet compliance was adequate in all patients except for in one patient (patient G). Despite poor compliance, the phenylalanine concentrations of this patient remained within the target range. The patients also visited our obstetric outpatient clinic. We frequently performed ultrasound to monitor growth and head circumference and to screen for structural abnormalities.

Two pregnancies were complicated by spontaneous abortion, and one pregnancy was by complicated by IUFD. This IUFD occurred at the gestational age of 27 wk because of severe fetal growth restriction that resulted from placental insufficiency. One woman delivered preterm at a gestational age of 36 wk. Neonatal anomalies consisted of a nonsynostotic occipital plagiocephaly, flattened left helix, mild hypertrophy of the left ventricle without hemodynamic consequences, a diastasis recti, and an umbilical hernia. One child (patient G) died 4 wk postpartum because of sudden infant death syndrome. An autopsy was refused. All neonatal sequelae are tabulated in Table 2.

### RESULTS

#### Study characteristics

A total of 196 pregnancies in 88 women were included. Dietary treatment was introduced in 70 of these pregnancies, of which dietary treatment was introduced in 30 pregnancies before conception. Dietary treatment in these pregnancies consisted of phenylalanine restriction and use of protein and vitamin supplements. The use of sapropterin was described in none of the patients. The target phenylalanine concentration of these diets varied; the upper limit had a median of 480\,\mu\text{mol}/L (range: 150–730\,\mu\text{mol}/L). In the treated group, phenylalanine concentrations were lower in each trimester than those in the untreated group (ratios of geometric mean phenylalanine concentrations in first, second, and third trimester were 1.5, 2.6, and 3.2, respectively; all $P < 0.001$). The presence of phenylketonuria or hyperphenylalaninemia in offspring was not thoroughly described.

#### Table 1

Case series in women with phenylketonuria or hyperphenylalaninemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>First author</th>
<th>Publication year</th>
<th>Untreated pregnancies</th>
<th>Treated pregnancies</th>
<th>Phenylalanine concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Maillot</td>
<td>2007</td>
<td>0</td>
<td>15</td>
<td>100–240</td>
</tr>
<tr>
<td>11</td>
<td>Knerr</td>
<td>2005</td>
<td>8</td>
<td>0</td>
<td>100–250; 120–360$^3$</td>
</tr>
<tr>
<td>12</td>
<td>Shaw-Smith</td>
<td>2004</td>
<td>3</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>Keller</td>
<td>2000</td>
<td>0</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>Kesby</td>
<td>1999</td>
<td>0</td>
<td>3</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>15</td>
<td>Koch</td>
<td>1998</td>
<td>1</td>
<td>0</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>16</td>
<td>Wilkinson</td>
<td>1998</td>
<td>1</td>
<td>4</td>
<td>360–600</td>
</tr>
<tr>
<td>17</td>
<td>Bachman</td>
<td>1993</td>
<td>2</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>Levy</td>
<td>1992</td>
<td>2</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>19</td>
<td>Tolmie</td>
<td>1992</td>
<td>8</td>
<td>0</td>
<td>50–150</td>
</tr>
<tr>
<td>20</td>
<td>Usha</td>
<td>1992</td>
<td>5</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>21</td>
<td>Superti-Furga</td>
<td>1991</td>
<td>2</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>22</td>
<td>Thompson</td>
<td>1991</td>
<td>0</td>
<td>1</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>23</td>
<td>Guttler</td>
<td>1990</td>
<td>2</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>24</td>
<td>Pullon</td>
<td>1990</td>
<td>2</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>25</td>
<td>Davidson</td>
<td>1989</td>
<td>0</td>
<td>9</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>26</td>
<td>Lynch</td>
<td>1988</td>
<td>0</td>
<td>4</td>
<td>100–400</td>
</tr>
<tr>
<td>27</td>
<td>Owada</td>
<td>1988</td>
<td>0</td>
<td>1</td>
<td>$&lt;420$</td>
</tr>
<tr>
<td>28</td>
<td>De Klerk</td>
<td>1987</td>
<td>4</td>
<td>4</td>
<td>$&lt;400$</td>
</tr>
<tr>
<td>29</td>
<td>Farquhar</td>
<td>1987</td>
<td>0</td>
<td>2</td>
<td>180–600</td>
</tr>
<tr>
<td>30</td>
<td>Rohr</td>
<td>1987</td>
<td>1</td>
<td>4</td>
<td>120–480</td>
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<tr>
<td>31</td>
<td>Matalon</td>
<td>1986</td>
<td>0</td>
<td>1</td>
<td>$&lt;360$</td>
</tr>
<tr>
<td>32</td>
<td>Soeters</td>
<td>1986</td>
<td>0</td>
<td>3</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>33</td>
<td>Lenke</td>
<td>1983</td>
<td>0</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td>34</td>
<td>Levy</td>
<td>1983</td>
<td>53</td>
<td>0</td>
<td>Unknown</td>
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<tr>
<td>35</td>
<td>Koch</td>
<td>1982</td>
<td>13</td>
<td>0</td>
<td>Unknown</td>
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<tr>
<td>36</td>
<td>Michels</td>
<td>1982</td>
<td>0</td>
<td>1</td>
<td>180–730</td>
</tr>
<tr>
<td>37</td>
<td>Lenke</td>
<td>1982</td>
<td>10</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>38</td>
<td>Levy</td>
<td>1982</td>
<td>3$^2$</td>
<td>3</td>
<td>Unknown</td>
</tr>
<tr>
<td>39</td>
<td>Tenbrinck</td>
<td>1982</td>
<td>0</td>
<td>2</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>40</td>
<td>Davidson</td>
<td>1981</td>
<td>0</td>
<td>1</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>41</td>
<td>Lorijn</td>
<td>1981</td>
<td>0</td>
<td>2</td>
<td>$&lt;600$</td>
</tr>
<tr>
<td>42</td>
<td>Blomquist</td>
<td>1980</td>
<td>6$^2$</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>43</td>
<td>Scott</td>
<td>1980</td>
<td>0</td>
<td>1</td>
<td>250–600</td>
</tr>
</tbody>
</table>

$^1$ Target phenylalanine concentration with treatment.

$^2$ Included one twin pregnancy.

$^3$ Maillot et al (10) describe 6 pregnancies in which 2 different target ranges for phenylalanine concentration were used.

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<table>
<thead>
<tr>
<th>Mother</th>
<th>Untreated phenylalanine</th>
<th>Gestational age at treatment introduction</th>
<th>Mean phenylalanine concentration</th>
<th>Pregnancy complications</th>
<th>Birth weight</th>
<th>Head circumference</th>
<th>Neonatal anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>250 µmol/L</td>
<td>8 wk</td>
<td>226 µmol/L</td>
<td>Uncomplicated</td>
<td>2710 g</td>
<td>33 cm</td>
<td>Nonsynostotic occipital plagiocephaly</td>
</tr>
<tr>
<td>B</td>
<td>209 µmol/L</td>
<td>13 wk</td>
<td>212 µmol/L</td>
<td>Preterm delivery</td>
<td>2895 g</td>
<td>33.5 cm</td>
<td>Mild concentric left hypertrophic ventricle, flattened helix of the left ear</td>
</tr>
<tr>
<td>C</td>
<td>490 µmol/L</td>
<td>4 wk</td>
<td>252 µmol/L</td>
<td>Uncomplicated</td>
<td>2945 g</td>
<td>35 cm</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>430 µmol/L</td>
<td>5 wk</td>
<td>271 µmol/L</td>
<td>Uncomplicated</td>
<td>3330 g</td>
<td>33 cm</td>
<td>Diastasis recti, umbilical hernia</td>
</tr>
<tr>
<td>E</td>
<td>430 µmol/L</td>
<td>Preconception</td>
<td>240 µmol/L</td>
<td>Spontaneous abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>1250 µmol/L</td>
<td>Preconception</td>
<td>167 µmol/L</td>
<td>Uncomplicated</td>
<td>3550 g</td>
<td>32 cm</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>311 µmol/L</td>
<td>Preconception</td>
<td>178 µmol/L</td>
<td>Intrauterine fetal death at gestational age of 27 wk</td>
<td>2995 g</td>
<td>34 cm</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>311 µmol/L</td>
<td>Preconception</td>
<td>112 µmol/L</td>
<td>Uncomplicated</td>
<td>3590 g</td>
<td>35 cm</td>
<td>Sudden infant death syndrome at 4 wk postpartum</td>
</tr>
<tr>
<td>G</td>
<td>311 µmol/L</td>
<td>7 wk</td>
<td>230 µmol/L</td>
<td>Uncomplicated</td>
<td>4300 g</td>
<td>36 cm</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>311 µmol/L</td>
<td>13 wk</td>
<td>311 µmol/L</td>
<td>Uncomplicated</td>
<td>3310 g</td>
<td>36 cm</td>
<td>None</td>
</tr>
</tbody>
</table>

Maternal Phenylketonuria

Table 2: Current case series: neonatal sequelae
although 13 neonates of the untreated group and 2 neonates of the treated group were diagnosed with phenylketonuria or hyperphenylalaninemia. Baseline characteristics are tabulated in Table 3.

Pregnancy complications

In the complete group, 16 spontaneous abortions, one molar pregnancy, 4 IUFDs, one pregnancy termination, and 13 preterm deliveries occurred (Table 4).

Untreated group

In the 126 untreated pregnancies, 10 women experienced first trimester loss (all spontaneous abortions). One pregnancy was terminated at the gestational age of 18 wk after severe FDs (eg, fused eyes) were diagnosed by ultrasound. The maternal phenylalanine concentration in this pregnancy was 960 µmol/L. One hundred fifteen pregnancies, with 2 sets of twins, resulted in the birth of 117 neonates. Two IUFDs occurred, both in mothers diagnosed with classical phenylketonuria; one IUFD occurred in the second trimester, and one IUFD occurred at 7 mo (both without a known cause). Five neonates were born preterm; the gestational age at birth was given for 4 neonates with a median of 35 wk (IQR: 34–36 wk).

Treated group

In the 70 treated pregnancies, there were 7 first-trimester losses (6 spontaneous abortions and one molar pregnancy). Sixty-three pregnancies resulted in the delivery of 64 neonates, and one of these pregnancies was a twin pregnancy. Two pregnancies resulted in IUFD. The first case was diagnosed in the second trimester. In this pregnancy, treatment was introduced before conception, although compliance was poor (mean phenylalanine concentration in the first trimester: 700 µmol/L). The second case of IUFD occurred because of severe fetal growth restriction at the gestational age of 27 wk (patient G; see Additional case series), whereas phenylalanine concentrations had been within the target range. A postmortem investigation showed no fetal anomalies, and placental insufficiency was confirmed. Eight neonates were born preterm with a median gestational age at birth of 34 wk (IQR: 31–36 wk).

Untreated compared with treated group

The occurrence of spontaneous abortion and IUFD was comparable between groups. Preterm delivery occurred less often

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Untreated pregnancies</th>
<th>Treated pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td>126</td>
<td>70</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Untreated pregnancies</th>
<th>Treated pregnancies</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td>126</td>
<td>70</td>
<td>1.0 (0.3, 3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>10</td>
<td>6</td>
<td>1.0 (0.3, 3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pregnancy termination</td>
<td>1</td>
<td>0</td>
<td>1.0 (0.3, 3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Molar pregnancy</td>
<td>0</td>
<td>1</td>
<td>1.0 (0.3, 3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Intrauterine fetal death</td>
<td>2</td>
<td>2</td>
<td>1.0 (0.3, 3.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>5</td>
<td>8</td>
<td>0.5 (0.1, 1.9)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

1 Untreated compared with treated.
2 Analyzed by using generalized estimating equations.
3 In 53 women and included 2 sets of twins.
4 In 45 women and included one twin pregnancy.
5 Median; IQR in parentheses (all such values).
in the untreated group, but this difference was not significant (OR: 0.5; P = 0.28).

**Relation to phenylalanine concentration per trimester**

There was no significant relation between the phenylalanine concentration per trimester and the occurrence of spontaneous abortion or preterm delivery, despite an OR of 1.7 (per doubling phenylalanine concentration) for the occurrence of spontaneous abortion (Table 5). Because of the small number of IUFDs, the relation between the phenylalanine concentration per trimester and the occurrence of IUFD could not be reliably evaluated.

**Neonatal sequelae**

In 196 pregnancies, 23 neonates were born SGA, and 58 neonates had microcephaly. Seven neonates were diagnosed with a CHD, and physical examination showed an FD in 20 neonates. IDDs were described in 49 neonates. Some neonates had more than one neonatal sequela (Table 6).

**Untreated group**

In the 117 neonates in this group, 19 neonates were born SGA, and microcephaly was present in 48 neonates. Five neonates were diagnosed with CHD (a double-chambered right ventricle, tetralogy of Fallot, ventricular septal defect, and 2 not further specified CHDs). Consequently, 2 of these neonates died at ages of 3 and 4 mo.

In 81 of the neonates, follow-up was described by means of an IQ or DQ; 38 neonates had an IDD (median age at testing: 8.0 y; IQR: 3.5–22.0). FDs were described in 14 neonates and consisted of the following: an underdeveloped philtrum, high palate, anteverted nostrils, broad flat nasal bridge, micrognathia, dysplastic ear helices, anteverted nares, receding forehead, deviated nasal septum, fused eyes, strabismus, epicanthal folds, and ptosis.

Other described neonatal anomalies or diseases were epilepsy or seizures in 7 neonates, brachydactyly and/or clinodactyly in 3 neonates, bifid thumbs in 2 neonates, esophageal atresia, bladder exstrophy, vertebral malformation, or renal anomaly in one neonate.

**Treated group**

As previously mentioned, two cases ended in an IUFD. Of the 62 remaining infants delivered, all but 2 infants survived; one stillbirth occurred because of intrapartum cord entanglement, and one neonate died of sudden infant death syndrome at the age of 4 wk (patient G; see Additional case series). Four neonates were born SGA, and 10 neonates had microcephaly. Two neonates were diagnosed with a CHD (coarctation of the aorta and mild concentric left hypertrophic ventricle). In 42 of the neonates, follow-up was described by means of an IQ or DQ; 11 neonates had an IDD (median age at testing: 3.5 y; IQR: 1.1–7.5 y). Six neonates had an FD.

Furthermore, the following isolated neonatal anomalies or diseases were described: cerebral palsy, seizures, pectus excavatum, polydactyly, clinodactyly, pyloric stenosis, and non-synostotic occipital plagiocephaly.

**Occurrence of CHD**

In the untreated group, but this difference was more frequent in the untreated group, but this difference was only significant for microcephaly and IDDs.

**Relation to phenylalanine concentration per trimester**

We describe the relation of phenylalanine concentration per trimester with the occurrence of neonatal sequelae in Table 7. A significant relation between the mean phenylalanine concentration in all trimesters and the occurrence of SGA, microcephaly, and IDDs was shown. The occurrence of CHD had ORs of 1.9–2.2 per doubling of the phenylalanine concentration per trimester; however, these ORs were not significant. Regarding FD, the first-trimester phenylalanine concentration was significantly related to its occurrence.

**DISCUSSION**

This study describes the largest untreated cohort of pregnancies with elevated phenylalanine concentrations since 1980 and provides an overview of reported pregnancy complications and neonatal sequelae and an unique comparison between untreated and treated pregnancies.

The results of our study suggested that maternal phenylalanine concentrations have no influence on the incidence of pregnancy complications. However, the number of pregnancy complications in our study was relatively small. For example, the number of spontaneous abortions was small, and although no statistical significance was shown, our results showed an OR of 1.7 per doubling phenylalanine in the first trimester (Table 5). Previous studies were also nonconclusive with some studies that showed a higher incidence of spontaneous abortion and other studies that did not show a higher incidence of spontaneous abortion (38, 45–47). To our knowledge, the relation between the phenylalanine concentration and IUFD or preterm delivery was not previously described in literature.

Regarding neonatal sequelae, our results followed the general pattern reported by other researchers, and in addition, we present

### Table 5

<table>
<thead>
<tr>
<th>Complication</th>
<th>First trimester</th>
<th></th>
<th>Second trimester</th>
<th></th>
<th>Third trimester</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>1.7 (0.9, 3.3)</td>
<td>0.073</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.1 (0.6, 2.0)</td>
<td>0.87</td>
<td>1.0 (0.6, 1.6)</td>
<td>0.95</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

1 Per doubling of the phenylalanine concentration.

2 Analyzed by using generalized estimating equations.
some remarkable findings. Our study showed that, as expected, the occurrence of microcephaly and IDDs is significantly higher in untreated pregnancies. The occurrence of CHD and FD was also higher, although not significant (Table 6). Furthermore, we showed that the mean phenylalanine concentration per trimester was significantly related to the occurrence of SGA, microcephaly, and IDDs (Table 7). Our results also showed that CHD occurred more frequently as the phenylalanine concentration per trimester doubled (OR per trimester: 1.9–2.2). This relation was not significant, probably because of the small number of CHDs. These results implied that the occurrence of these neonatal sequelae was related to the height of phenylalanine concentrations, with an increased occurrence in case of doubling phenylalanine concentrations.

Our finding that FD was only related to the mean phenylalanine concentration in the first trimester is remarkable (Table 7).

Multivariate analysis of phenylalanine concentration per trimester also showed a significant association with FD only for the first trimester ($P = 0.017$; second and third trimesters $P > 0.35$; data not shown). These results implied that, if treatment is started after the first trimester, FD cannot be averted. In theory, this finding may be easily explained because the development of all major organs, as well as the formation of the face, is completed by the end of the first trimester (48). Similar findings could be expected for the occurrence of CHD.

Because phenylalanine concentrations in the 3 trimesters were strongly correlated in individual patients, no separation of the associations of the phenylalanine concentration per trimester with SGA, microcephaly, CHD, and IDDs was possible (data not shown).

Previous literature, including the international Maternal Phenylketonuria Collaborative Study, reported that elevated maternal phenylalanine concentrations resulted in maternal phenylketonuria syndrome with the following neonatal sequelae: low birth weight, microcephaly, CHD, IDDs, and FD (6–10, 47, 49–51). Lenke and Levy (51) investigated offspring of untreated women with classic phenylketonuria. In their study (51), 40% of neonates weighed <2500 g, 73% of neonates had microcephaly, 12% of neonates had a CHD, and 92% of neonates were intellectually disabled. In our study, these numbers were slightly smaller, possibly because of inclusion of more women with mild phenylketonuria or hyperphenylalaninemia instead of classic phenylketonuria. In the untreated group in our study, 19.2% of neonates were SGA, 46.2% of neonates had microcephaly, 6.6% of neonates had a CHD, and 92% of neonates had IDDs.

Consistent with our results, previous studies showed that maternal phenylalanine concentrations were related to the occurrence of all neonatal sequelae (38, 46, 51). In our study, this relation was not significant for CHD, probably because of the small numbers of CHD.

Levy et al (52) described 48 women diagnosed with hyperphenylalaninemia (untreated phenylalanine <600 μmol/L) with 50 untreated pregnancies. Levy et al (52) showed all measures (birth weight, length, and head circumference) were within normal limits in these 50 neonates. Only one neonate was diagnosed with CHD. In our study, we included 47 hyperphenylalaninemia pregnancies that resulted in offspring, and 37 of these pregnancies remained untreated. In the latter group, one neonate was SGA (birth weight was known for 29 neonates), and
microcephaly was present in 5 of 33 neonates of which head circumference was available. No CHD was detected. The results of Levy et al (52) implied that mainly the highly elevated phenylalanine concentrations cause fetal sequelae. Our study supports this implication, although we still showed 15.2% microcephaly in offspring of hyperphenylalaninemia women; this percentage was higher than the findings of Levy et al (52) in hyperphenylalaninemia women but lower than the 46.2% we showed in the complete group.

For data collection, we included cases derived from published case reports and case series. Publication bias may have influenced our data. Because case reports with adverse neonatal outcome are more likely to be published, this likelihood may have resulted in a higher incidence of neonatal sequelae in our study. Another limitation of this study was that the number of events in our study were relatively small. Therefore, it was not reliable to test for significance with the occurrence of IUFD, whereas a significance for the relation between phenylalanine concentrations and CHD may have been concealed. Unfortunately, other pregnancy complications such as gestational diabetes and preeclampsia were often not or inaccurately described and could not be analyzed. Because values of the mean phenylalanine concentration per trimester were collected from text, tables, or graphics, these values were estimates. It is not likely that these estimates influenced our results grossly. Finally, the occurrence of spontaneous abortion might have been underreported because the obstetric history of included patients was not mentioned in every article.

To our knowledge, we presented the largest combined series of pregnancies in untreated mothers with phenylketonuria and hyperphenylalaninemia in the literature since 1980. In conclusion, this study underlines the importance of treatment of hyperphenylalaninemia to prevent pregnancy complications and maternal phenylketonuria syndrome (SGA, microcephaly, CHD, IDDs, and FD) in neonates. The study also implies that treatment should be started before the first trimester to prevent FD.

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The authors’ responsibilities were as follows—JJD and BWP: designed the research; BWP: conducted data collection; BWF and WCH: performed statistical analysis; JJD and BWP: wrote the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES