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Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease

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ABSTRACT
Objective: We studied the reciprocal effect of pregnancy and von Hippel-Lindau (VHL) disease by analyzing the influence of pregnancy on VHL disease-related lesions and VHL disease on pregnancy outcome.

Methods: Medical charts and imaging reports from the VHL disease expertise centers in the Netherlands were used to retrospectively assess lesion progression score before and after pregnancy and to obtain data on pregnancy outcome and VHL disease-related lesions. The Friedman test was used for analysis (p ≤ 0.05). Twenty-nine patients were studied (48 pregnancies, 49 newborns).

Results: The progression score of cerebellar hemangioblastomas significantly changed between the single MRI scan before and the 2 scans after pregnancy (p = 0.049) (n = 12). Fetal mortality rate was 2% (n = 1) caused by maternal pheochromocytoma. Maternal VHL disease-related complications occurred in 17% (n = 8) of all pregnancies. In 4 patients, a life-threatening situation emerged: hydrocephalus due to cerebellar hemangioblastoma (n = 2) and pheochromocytoma (n = 2).

Conclusions: Pregnancy in patients with VHL disease induces cerebellar hemangioblastoma progression and causes a high VHL disease-related pregnancy complication rate. We recommend intensified surveillance of patients with VHL disease, especially of cerebellar hemangioblastomas during preconception care and pregnancy. Neurology® 2012;79:793–796

GLOSSARY
RCC = renal cell carcinoma; VHL = Von Hippel-Lindau.

Von Hippel-Lindau (VHL) disease is inheritable and associated with the development of multiple well-vascularized tumors throughout life. The onset of disease occurs at a mean age of 26 years (range 1–70 years).1 Hemangioblastomas are frequently found during adolescence, developing in the retina, cerebellum, spinal cord, supratentorial region, and brainstem. In the visceral organs, pheochromocytomas, renal cell carcinoma (RCC) and renal cysts, pancreatic islet cell tumors, and cysts occur.1 International guidelines recommend intensive surveillance to detect tumors in an early stage.1 Although triggers for VHL disease tumor progression are unknown, cerebellar hemangioblastomas are reported to oscillate between periods of growth and stability.2 In addition, several case studies show that pregnancy or delivery in patients with VHL disease can be complicated by CNS hemangioblastoma or pheochromocytoma with consequences for maternal and neonatal outcome.3–5 One retrospective study based on a ques-

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tionnaire from 30 patients with VHL disease described a 5% self-reported VHL-related maternal morbidity. Progression of VHL lesions during pregnancy could be explained by several factors. A rise in venous pressure by increased circulating blood volume and compression of the vena cava inferior to the growing uterus could be responsible for growth of hemangioblastomas. In addition, estrogen-induced endothelial proliferation is thought to stimulate stromal hemangioblastoma cell growth, and progesterone may increase venous distensibility. Placental-derived angiogenic factors might add to hemangioblastoma growth because proangiogenic factors are present in the maternal circulation.

We aimed to study the reciprocal effect of pregnancy and VHL disease by analyzing the influence of pregnancy on VHL disease-related lesions and of VHL disease on pregnancy outcome.

METHODS Subjects. We retrospectively studied 29 of 31 women with VHL disease who were receiving surveillance in VHL disease expertise centers in the Netherlands. The surveillance includes funduscopy, MRI of the spinal cord and cerebellum, CT scan or ultrasound of the abdomen, and determination of plasma and urine levels of metanephrines. Diagnosis of VHL disease was based on clinical criteria or confirmed by germline mutation testing. Clinical criteria were met by either a positive family history of VHL disease with a personal history of at least one CNS hemangioblastoma, a case of RCC, or one pheochromocytoma or a personal history of 2 or more CNS hemangioblastomas or one CNS hemangioblastoma with a VHL disease-associated visceral lesion.

Measurements. The influence of VHL disease on pregnancy-related outcome and the influence of pregnancy on VHL disease activity were scored using the following parameters: 1) VHL disease-related complaints, number of VHL disease-related interventions, and size and number of individual VHL lesions; and 2) pregnancy-related fetal and maternal mortality and morbidity, VHL disease-associated and VHL disease-unrelated (e.g., pregnancy-related hypertensive disorders).

Data concerning VHL lesions leading to interventions or complaints before, during, and after pregnancy of all patients were extracted from medical records and completed by telephone interview or during outpatient clinic visits.

Data on all interventions performed within 4 years before and 4 years after pregnancy were collected. The severity of complaints before, during, and after pregnancy was subjectively scored as follows: 1 (no complaints), 2 (stable), 3 (progressive), and 4 (loss of function). Imaging reports (MRI scan, CT scan, ultrasound, or funduscopy), available for 15 pregnancies, were used to assess the effect of pregnancy on individual lesions in the cerebellum, spinal cord, retina, kidney, and pancreas. One or 2 measurements before and 1 or 2 measurements after pregnancy were collected with a maximum time span ranging from 4 years before the last menstruation until 4 years after delivery. Organ involvement was scored with a lesion progression score as follows: 1 (no lesions), 2 (stable), 3 (progression in number or size), or 4 (progression in number > 2 or > 2 cm in size, for retinal lesions threatened vision). The score 5 was noted when CNS and retinal lesions caused a life-threatening situation or blindness. Pheochromocytomas were scored as absent or present. In this design, patients served as their own control.

Standard protocol approvals, registrations, and patient consents. Patient identity was protected by unique patient identifiers; codes were known only to 2 database managers. According to Dutch law no further institutional review board approval was required. All subjects provided written informed consent to participate in the study.

Statistical analysis. Statistical analysis was performed by the Friedman test ($p \leq 0.05$).

RESULTS All 31 patients with VHL disease with at least one delivery known in the VHL disease centers were approached between April and September 2010. Two patients were excluded for personal and cognitive reasons, resulting in 29 patients and 48 pregnancies with 49 newborns (table 1). The women delivered between 1966 and 2010; 60% delivered after 1990.
Maternal VHL disease-related complications occurred in 17% (n = 8) of all pregnancies (table 2); in half of the women VHL disease was diagnosed before their pregnancy. In those 8 pregnancies, 10 VHL lesions led to new or increased complaints or intervention: hemangioblastoma cerebellum (n = 2) and spinal cord (n = 1), pheochromocytoma (n = 2), RCC (n = 1), and retinal angioma (n = 4, 3 of which with major impaired vision loss/ablation). In 4 patients, a life-threatening situation emerged: cerebellar hemangioblastoma and hydrocephalus (n = 2) and pheochromocytoma (n = 2) (figure), resulting in 1 fetal death and 2 premature deliveries by cesarean section. All VHL disease complications occurred during a first pregnancy; 7 of these 8 patients did not pursue another pregnancy. Of the patients without a VHL disease complication, 67% had another pregnancy. The severity of VHL disease-related patient complaints during pregnancy (n = 48) was significantly increased (p = 0.005). VHL disease interventions during pregnancy (n = 7) and in the first year after delivery (n = 8) were more frequent than those in the 4 years before pregnancy (average n = 3).

Imaging-based progression scores of VHL disease-related lesions showed in the cerebellum a significant change of progression in the period between 1 MRI scan before and 2 MRI scans after pregnancy (p = 0.049). An increase in the progression score in

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**Table 2** VHL disease complications during pregnancy

<table>
<thead>
<tr>
<th>Patient</th>
<th>VHL disease known during pregnancy (yes/no)</th>
<th>Lesion</th>
<th>Complaints</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Bilateral pheochromocytoma (revealed after delivery)</td>
<td>None</td>
<td>Bilateral adrenalectomy (6 mo after delivery)</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>Bilateral pheochromocytoma</td>
<td>Nausea, headache, sweating, abdominal pain</td>
<td>Cesarean section combined with adrenalectomy (28 wk of gestation)</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Cerebellar hemangioblastoma and hydrocephalus</td>
<td>Headache, vomiting, vertigo, balance disturbance, diplopia</td>
<td>Cesarean section combined with craniotomy (35 wk of gestation)</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Cerebellar hemangioblastoma and hydrocephalus</td>
<td>Headache, vomiting; later on balance disturbance, speech disorder, muscle weakness</td>
<td>Craniotomy (1 wk after delivery)</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Spinal cord hemangioblastoma</td>
<td>Radiating lower back pain</td>
<td>Resection hemangioblastoma (6 mo after delivery)</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Renal cell carcinoma</td>
<td>None</td>
<td>Partial nephrectomy rightsided (20 wk of gestation)</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Ablatio retinae: papillary angioma (known before pregnancy)</td>
<td>Visual field loss</td>
<td>Vitrectomy (10 wk of gestation)</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Ablatio retinae: angioma (known before pregnancy)</td>
<td>Total vision loss</td>
<td>None</td>
</tr>
</tbody>
</table>

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**Figure** MRI cerebellum, cerebellar hemangioblastoma, and hydrocephalus complicating pregnancy

(A, B) Lesion on the right side of the cerebellum 3 months before pregnancy, during a routine VHL disease screening, measuring 0.5 cm (with gadolinium). (C) The same lesion at 32 weeks of gestation on the right side of the cerebellum, measuring a central component of 2.7 cm with a cystic component of 4 cm (table 2, patient 3).
the first measurement early after pregnancy has been measured at a mean of 6.4 months after delivery and can be considered as an effect of pregnancy. A decrease in progression score was found in the second MRI scan after pregnancy 1 year later (mean 18.7 months after delivery). In other organs, no significant progression of lesions was found.

Maternal mortality rate was 0%; fetal death occurred in one patient (2%) at a gestational age of 32 weeks, caused by maternal hypertension from pheochromocytoma. Maternal pregnancy-related complications occurred in 15% of pregnancies (n = 7); pregnancy-related hypertensive disorders were seen in 12.5% of patients (n = 6), and one patient has intrahepatic cholestasis of pregnancy.

DISCUSSION Increased activity of VHL disease, in particular of cerebellar hemangioblastomas, was observed in pregnancy. In 17% of patients, VHL disease-related complications were observed; VHL disease was diagnosed in only half of the patients before pregnancy. Four of 8 complicated pregnancies resulted in a life-threatening situation for mother and child (with one fetal death). Previously a VHL disease-related morbidity during pregnancy of 5.4% was found. However, these data were derived from a written questionnaire sent to patients randomly. In our study, data were derived from medical reports, and all mothers with the diagnosis of VHL disease in the Dutch VHL disease expertise centers were evaluated.

Our result of cerebellar hemangioblastoma progression during pregnancy is in line with preliminary data showing a significantly higher complication rate for hemangioblastomas in patients with VHL disease with at least one pregnancy. Possible explanations are the hormonal (growth factors and estrogen) and hemodynamic changes occurring during pregnancy, adding to the preexisting increased vascular endothelial growth factor expression (a direct downstream effect of biallelic VHL gene inactivation). Therefore, a direct relationship between pregnancy and progression of cerebellar hemangioblastomas is likely. VHL disease-related lesions in other organs showed no significant change in progression score after pregnancy. This finding may be explained by the few patients with specific lesions and the age at onset of other VHL disease manifestations. In addition, the retrospective setting and the small sample size limit this study. However, larger series in this rare disease are difficult to achieve.

Our results show growth of VHL cerebellar hemangioblastomas during pregnancy and a high VHL disease complication rate during pregnancy. Intensi-
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