The most frequent neoplasms found in patients with VHL disease are CNS hemangioblastomas (80% of VHL disease patients harbor these tumors).² Sporadic and VHL-associated hemangioblastomas are nearly always (more than 95% of the time) found infratentorially in the spinal cord, brainstem, or cerebellum.²⁵ Patients will frequently harbor a number of hemangioblastomas, and new tumors develop over their life span.¹²⁵ Despite the complex, protean, and progressive nature of VHL disease–associated hemangioblastomas, many of these neoplasms will not become symptomatic and consequently will not require resection.¹ Nevertheless, CNS hemangioblastomas can lead to significant morbidity and mortality in VHL patients.¹⁵,²¹ Hemangioblastomas can grow and/or develop peritumoral edema/cysts, becoming symptomatic and requiring resection.²⁷ To minimize irreversible tumor-associated neurological deficits while avoiding unnecessary surgery, early symptom development is an indication for resection of CNS hemangioblastomas in patients with VHL disease.⁸,¹³,²⁶ Consequently, the identification of risk factors that are associated with the development of tumor-related...
Hemangioblastomas in pregnancy

Symptomatology is critical to the optimal management of CNS hemangioblastomas. Case reports have suggested that pregnancy may accelerate tumor and/or peritumoral cyst development and growth, resulting in an increased risk of neurological symptom development during pregnancy and need for resection. Further, the perceived increased risk of hemangioblastoma development and progression during pregnancy has led some to advocate prophylactic resection of asymptomatic hemangioblastomas or forgoing pregnancy in VHL disease patients with multiple CNS hemangioblastomas. To determine the effect of pregnancy on CNS hemangioblastoma and/or peritumoral cyst development and growth and to optimize management of VHL disease patients wanting to become pregnant and those who are pregnant, we prospectively analyzed cases in which women with VHL disease became pregnant, using serial clinical and imaging evaluation and comparing these findings to prospective serial clinical and imaging findings in a cohort of female patients with VHL disease who did not become pregnant.

Methods

Patients

Female patients of anticipated reproductive age (between the age of 16 and 35 years at study entrance) who were enrolled in a study that prospectively examines the natural history of VHL disease-associated CNS neoplasms (NIH #00-N-0140) with 1 year or more of follow-up were included (total accrual ceiling of 250 patients). Patients were confirmed to have VHL disease using clinical and/or genetic criteria. 11

Patient Demographics

Clinical Evaluation. Serial evaluations (clinical and radiological) were performed at 6- to 12-month intervals, including during the prepregnancy and postpartum periods in patients who became pregnant. Patients who became pregnant had their serial clinical and imaging evaluations delayed until after delivery. Clinical findings, including detailed neurological examinations were performed and recorded at each visit.

Imaging Evaluation. Identification and quantification of hemangioblastomas and/or associated edema/cysts were determined by craniospinal MRI. High-resolution, postcontrast T1-weighted, FLAIR, spoiled gradient-recalled acquisition, and T2-weighted sequences were analyzed.

Tumor volumes were measured using contrast-enhanced T1-weighted MRI and calculated at each visit using a modified ellipsoid formula: (largest width × largest height × largest length) × 0.5. 14 Volumes of peritumoral cysts of the cerebellum were calculated in a similar manner using T2-weighted MRI sequences. Because contrast-enhancing foci less than 3 mm in diameter can often be blood vessels, lesions below this size threshold at last follow-up were not considered tumors.

Statistical Analysis

Demographic information was collected for each patient including age, ethnicity, height, weight, presence of other VHL disease–related neoplasms, number of hemangioblastomas, number of hemangioblastomas treated, and time to treatment (if needed) after pregnancy. Hemangioblastomas were characterized by their anatomical location, number of pregnancies exposed, maximum volume, associated peritumoral cyst(s), and need for resection. Annualized tumor growth rates were calculated from the logarithmic difference in tumor volume and the time interval between evaluations to account for exponential growth in absolute tumor volume. Annualized peritumoral cyst growth rate was calculated in a similar manner for all cysts with demonstrated growth greater than 1 year. All statistical analyses were performed with JMP 9 (SAS).

Results

Patient Demographics

There were 131 female patients enrolled in the prospective natural history study. Thirty-six female patients with more than 1 year of follow-up and between the age of 16 and 35 years upon entry into the study were identified. Nine of these patients (25%) became pregnant a total of 13 times. Their mean age (±SD) at pregnancy was 29.2 ± 3.8 years (range 20–35 years). The 9 pregnant patients represent all the patients who became pregnant in the study during the evaluation period. There were a total of 177 hemangioblastomas in both cohorts (32 [22% of all tumors] in the pregnancy cohort and 145 [78%] in the no-pregnancy cohort). The clinical and demographic characteristics of the pregnancy and no-pregnancy cohorts were not significantly different (Table 1).

Hemangioblastoma Characteristics

Pregnancy Cohort. Thirty-two hemangioblastomas were identified in the 9 patients in the pregnancy cohort. There were 20 cerebellar (63% of all hemangioblastomas in the pregnancy cohort), 2 brainstem (6%), 9 spinal cord (28%; 3 cervical, 6 thoracic), and 1 cauda equina (3%) hemangioblastomas. The mean tumor volume at last follow-up or immediately before resection was 215.5 ± 637.5 mm³ (median 34.0 mm³). Seven hemangioblastomas (22%; 5 cerebellar, 1 brainstem, 1 spinal cord) had associated peritumoral cysts. The mean cyst volume at the last follow-up visit or immediately before resection was 5259.8 ± 6323.3 mm³ (median 2059.0 mm³).

Twenty-nine hemangioblastomas (91% of the total number of tumors identified in the pregnancy cohort) were present during a pregnancy. The mean tumor volume measured at the first follow-up imaging evaluation after pregnancy was 97.8 ± 462.7 mm³ (median 14.5 mm³). Five of these hemangioblastomas (17%; 4 cerebellar, 1 brainstem) had associated peritumoral cysts. The mean peritumoral cyst volume at the first follow-up after pregnancy was 2634.7 ± 6501.3 mm³ (median 86.1 mm³).

No-Pregnancy Cohort. The 27 patients in the no-pregnancy cohort harbored 145 hemangioblastomas during the observation period. The mean tumor volume was 331.6 ± 952.6 mm³ (median 45.9 mm³) at last follow-up or
immediately before resection. There were 74 cerebellar (51%), 13 brainstem (9%), 46 spinal cord (32%; 20 cervical, 26 thoracic), 3 supratentorial compartment (2%), and 9 cauda equina (6%) hemangioblastomas. Twenty-three tumors (15.8%; 12 cerebellum, 7 spinal cord, 3 brainstem, 1 cauda equina) were associated with peritumoral cysts. Mean cyst volume at last follow-up was 1535.2 ± 1974.2 mm³ (median 517.9 mm³).

Hemangioblastoma Development

The mean rate of new tumor development during pregnancy (0.4 ± 0.4 tumors/year) was similar to the mean rate of tumor development during the nonpregnant period (0.3 ± 0.4 tumors/year; paired t-test, p = 0.08) in the pregnancy cohort. The mean rate of new tumor development in the no-pregnancy cohort was similar (0.3 ± 0.5 new tumors/year, t-test, p = 0.6) to that in the pregnancy cohort during pregnancy and nonpregnant periods (Fig. 1).

Hemangioblastoma Growth

Ten hemangioblastomas were exposed to a single pregnancy and 19 tumors (66% of tumors) were exposed to 2 separate pregnancies. The mean annualized growth rate during the pregnancy period was 29.8% ± 42.7% of the previous volume per year. The mean annualized growth rate was 41.4% ± 51.4% of the previous volume per year for the same tumors when the women were not pregnant (Fig. 1). There was no statistically significant difference between the growth rate of these tumors during pregnancy and their growth rate when the patients were not pregnant (paired t-test, p = 0.9). Moreover, these growth rates were not significantly different (t-test, p = 0.6) from the tumor growth rate (34.3% ± 55.3%) in the no-pregnancy cohort.

Peritumoral Cyst Development

The mean rate of hemangioblastoma-associated peritumoral cyst development during pregnancy (0.1 ± 0.2 cysts/year) was similar to the mean rate of cyst development during the nonpregnant period (0.1 ± 0.1 cysts/year, paired t-test, p = 0.9) in the pregnancy cohort. The mean rate of new cyst development in the no-pregnancy cohort was similar (0.1 ± 0.2 cysts/year; t-test, p = 0.7) to that of the pregnancy cohort during pregnancy and nonpregnant periods (Fig. 1).

Peritumoral Cyst Progression

The mean rate of hemangioblastoma-associated peritumoral cyst development during pregnancy (0.1 ± 0.2 cysts/year) was similar to the mean rate of cyst development during the nonpregnant period (0.1 ± 0.1 cysts/year; paired t-test, p = 0.9) in the pregnancy cohort. The mean rate of new cyst development in the no-pregnancy cohort was similar (0.1 ± 0.2 cysts/year; t-test, p = 0.7) to that of the pregnancy cohort during pregnancy and nonpregnant periods (Fig. 1).

Need for Treatment

Before pregnancy, 3 hemangioblastomas became symptomatic and were resected. Six additional hemangioblastomas (21%) ultimately required resection after a pregnancy. Four hemangioblastomas that required resection had associated peritumoral cysts. The mean time to
Hemangioblastomas in pregnancy

The mean patient age at resection of all 9 hemangioblastomas in the pregnancy cohort (30.2 ± 2.6 years, range 26–34 years) did not differ significantly (t-test, p = 0.3) from the mean age at resection of 28 hemangioblastomas in the no-pregnancy cohort (32.3 ± 5.6 years, range 19–41 years). Thirteen of the hemangioblastomas resected in patients in the no-pregnancy cohort had associated peritumoral cysts.

Discussion

Previous Reports

Previous case reports have suggested that pregnancy is linked to symptomatic progression of hemangioblastomas and/or peritumoral cysts and, ultimately, the need for resection. Specific studies have suggested that hemodynamic and hormonal changes during pregnancy increase the risk of new tumor development and symptomatic growth of hemangioblastomas in expectant mothers. However, no data have demonstrated that these mechanisms actually occur in vivo. Despite the lack of tangible evidence, pregnancy continues to be cited as a significant risk factor for the development of hemangioblastoma-associated symptoms and, ultimately, the need for surgery. To best define the effect of pregnancy on hemangioblastoma development and progression, we prospectively examined the effect of pregnancy on the development and growth of CNS hemangioblastomas in patients with VHL disease.

Current Report

Radiological evidence demonstrates that new hemangioblastomas consistently arise in VHL disease patients at a variable and unpredictable rate as a part of the natural history of the disease. Radiological evidence also suggests that pregnancy may be associated with an increase in the rate of tumor development and symptomatic growth of hemangioblastomas.

Fig. 1. A: Annualized rates of new tumor development of hemangioblastomas in patients who became pregnant (pregnancy cohort) during their pregnant and nonpregnant periods, as well as in patients who did not become pregnant (no-pregnancy cohort). The rate of tumor development over time did not differ significantly between pregnancy and nonpregnant periods in the patients who became pregnant or between patients who became pregnant compared with those who did not. B: Annualized relative growth rates of hemangioblastomas in pregnant patients during their pregnant and nonpregnant periods, as well as in patients who did not become pregnant. The tumor growth rate did not differ significantly between pregnant and nonpregnant periods in the patients who became pregnant or between patients who became pregnant compared with those who did not. C: Annualized rates of new hemangioblastoma-associated peritumoral cyst development in pregnant patients during their pregnant and nonpregnant periods, as well as in patients who did not become pregnant. The rate of cyst development over time was not significantly different between pregnant and nonpregnant periods in the patients who became pregnant or between patients who became pregnant and those who did not. D: Annualized relative growth rates of hemangioblastoma-associated peritumoral cysts in pregnant patients during their pregnant and nonpregnant periods, as well as in patients who did not become pregnant. There was no significant difference in cyst growth rate over time during pregnancy and nonpregnant periods in the patients who became pregnant or between the patients who became pregnant and those who did not. There was a statistically significant difference between the growth rate during nonpregnant periods in the patients who became pregnant and the growth rate in patients who did not become pregnant. Error bars represent standard error. N.S. = not significant.
disease. The current study findings indicate that the development of new hemangioblastomas in VHL disease patients who become pregnant does not differ from the background development of new tumors in same-age female patients who do not become pregnant. The lack of additional new hemangioblastomas on serial imaging indicates that the proliferative signals presumed to exist during pregnancy do not play a clinically detectable role in modifying the developmental pathways in hemangioblastomas. Moreover, the rate of development of hemangioblastomas seen in these patients is similar to previous reports of VHL patients across sex and age.

**Hemangioblastoma Growth.** Previous VHL disease studies examining the natural history of CNS hemangioblastomas demonstrate that these lesions grow in a salatory pattern that is characterized by alternating periods of growth and quiescence. While we observed hemangioblastomas at different stages of their growth, the long-term growth rate of both small and large tumors follows an exponential curve that mirrors the biology of dividing tumor cells, allowing us to compare the proliferation rate of neoplastic cells in hemangioblastomas of any size. Comparison of relative growth rates of hemangioblastomas at different stages of their growth, the long-term growth rate of both small and large tumors follows an exponential curve that mirrors the biology of dividing tumor cells, allowing us to compare the proliferation rate of neoplastic cells in hemangioblastomas of any size. Comparison of relative growth rates of hemangioblastomas in patients with VHL disease revealed that the rate of growth of tumors in patients who became pregnant does not differ significantly from the rate of growth of tumors in those who did not. Furthermore, within the same patient, the rate of tumor growth does not differ significantly between pregnancy and the nonpregnant state.

These findings indicate that while hemodynamic and hormonal changes occur during pregnancy, they do not appear to alter the growth of hemangioblastomas in VHL disease. A potential reason for the previous perceived increase in progression and symptom development of hemangioblastomas during pregnancy may be related to the fact that many pregnancies occur during the most common age for development of symptoms associated with hemangioblastomas. Prior reports describe the mean age for symptom development associated with CNS hemangioblastomas in VHL disease as approximately 33 years in both men and women, which is similar to the mean age at pregnancy in the current study (30 years) and is within the age range during which patients became pregnant (20–35 years). Moreover, the infrequent management of hemangioblastoma-associated symptoms in VHL disease and sporadic cases during pregnancy may have led to its description as a relatively unique event in the literature, despite the fact that it coincides with the natural history of hemangioblastoma symptom formation.

**Peritumoral Cyst Development.** Peritumoral cysts are caused by increased permeability of tumor vessels that causes leakage of plasma ultrafiltrate into the immediately surrounding nervous system tissues. The increased peritumoral fluid manifests initially as edema, but after the resorptive capacity of the neural tissue is exceeded, a cyst forms. Peritumoral cysts often progress in size much faster than the hemangioblastoma and, consequently, they most frequently underlie symptom development in VHL disease. However, the rate of new peritumoral cyst development did not differ significantly between pregnant and nonpregnant periods or pregnancy and no-pregnancy cohorts, indicating that pregnancy does not appear to have an effect on the development of new peritumoral cysts.

**Peritumoral Cyst Progression.** Based on mechanisms of peritumoral cyst development and progression, the hemodynamic changes (expansion of maternal blood volume and compression of inferior vena cava) that occur in pregnancy have been proposed to lead to increased edema and cyst expansion, which can result in symptom development. Cyst growth rates during pregnancy were similar to the growth rates during the entire observation period in the no-pregnancy cohort, suggesting that any expansions in cyst volume follow a natural course of cyst progression. Furthermore, none of the peritumoral cysts present before pregnancy regressed or remained stable for prolonged periods after pregnancy. This indicates that pregnancy-associated expansion of the intravascular volume and increased venous pressure due to compression of the inferior vena cava do not have a clinically relevant effect on cyst expansion. Moreover, the cysts in the pregnancy cohort had a significantly greater rate of growth during nonpregnant periods than during pregnancy periods, providing additional evidence to indicate a lack of cyst progression due to pregnancy-induced biological phenomena.

**Clinical Implications of Pregnancy in VHL Disease.**

Von Hippel-Lindau disease is a multiorgan neoplastic syndrome that affects the adrenal glands, pancreas, kidneys, reproductive adnexal organs, retina, and craniospinal axis. Despite being benign, CNS hemangioblastomas represent a significant cause of morbidity as well as mortality in patients with VHL disease. Although Wanebo and colleagues attempted to characterize the features that were linked to symptom development, sensitive and specifi-
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...ic thresholds for size or tumor growth were not identified. Therefore, the current recommended clinical management of CNS hemangioblastomas in VHL disease remains serial observation with imaging and resection only after development of associated symptoms or signs.

Based on reports of the potential increased risk of hemangioblastoma development and progression during pregnancy, prophylactic resection of asymptomatic hemangioblastomas or avoiding pregnancy in patients with VHL disease and multiple CNS hemangioblastomas has been advocated by some. The current findings, however, indicate that development and growth of hemangioblastomas in pregnant patients with VHL disease does not differ from that in nonpregnant female patients and that fecond female VHL disease patients should be managed similarly to their male counterparts with regard to CNS hemangioblastomas. Specifically, serial clinical and imaging follow-up at up to 2-year intervals or upon symptom development is recommended.

Nevertheless, consistent follow-up during pregnancy is not feasible, as pregnant patients do not undergo MRI with contrast due to the lack of established guidelines safeguarding the fetus. Additionally, surgical intervention for symptomatic hemangioblastomas in pregnant patients, if necessary, is made more complex by the presence of the fetus. Successful management of symptomatic patients during pregnancy has been reported, but recommendations regarding the timing of surgical intervention, anesthesia, and delivery of the fetus vary considerably depending on the stage of pregnancy. Therefore, serial imaging of prospective mothers with VHL disease before conception and after delivery, with resection of symptomatic hemangioblastomas appears to be a most reasonable management approach.

Conclusions

Pregnancy is not associated with increased hemangioblastoma or peritumoral cyst development or progression in women with VHL disease. As in other VHL disease patients, asymptomatic CNS hemangioblastomas in fecund patients can be managed expectantly.

Disclosure

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