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Editorial

Von Hippel-Lindau disease and pregnancy

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Hemangioblastomas associated with von Hippel-Lindau (VHL) disease are thought to exhibit accelerated tumor growth, progression, and cyst formation in pregnancy, although the mechanism is poorly understood.[2,5,8–10] Pregnancy is known to aggravate brain tumors by 3 mechanisms: acceleration of growth, increased edema, and immunotolerance to foreign antigens.[1] Von Hippel-Lindau disease is an autosomal dominant neurocutaneous dysplastic condition found on chromosome 3p25-26.[6–8] The *VHL* gene is involved in expression of VEGF, making it important for normal extraembryonic vasculogenesis.[3] Hemangioblastomas are composed of endothelium and stromal cell components.[12] Pregnancy results in a high estrogen state, which stimulates endothelial proliferation and has been associated with growth of hemangiomas despite the lack of estrogen receptors in the lesions.[5,11] Grimbert et al.[4] performed a retrospective study of 30 women with 56 pregnancies and found a 96.4% survival rate and suggested that pregnancy should not be discouraged for patients with VHL disease. When these patients do become symptomatic, several case reports have shown that symptomatic lesions can be safely resected in pregnancy.[2,8–10] Finally, symptomatology from cerebellar hemangioblastomas is an indication for surgery in VHL disease and occurs at a mean age of 33 years.[7,12]

In their article, Ye et al.[13] address the effect of pregnancy on hemangioblastomas in the setting of VHL disease. They performed a prospective study with serial clinical and imaging in patients with VHL disease who became pregnant and compared findings during pregnancy with findings obtained during the time that these women were not pregnant. They also compared these findings with those of a separate cohort of patients with VHL disease who did not become pregnant during the study period. Thirty-six consecutive female patients between 16 and 35 years of age were included, with a total of 177 hemangioblastomas. The mean follow-up period ± SD was 7.5 ± 2.3 years. Serial evaluations at 6- and 12-month intervals were performed before and after pregnancy. Craniospinal MRI was used for identification and quantification of the number of hemangioblastomas, cysts, and peritumoral edema. Tumor volumes were calculated using a modified ellipsoid formula at each visit. In the pregnancy cohort, there were 20 cerebellar, 2 brainstem, and 9 spinal cord hemangioblastomas. In the no-pregnancy cohort, there were 27 patients with 145 hemangioblastomas. In the pregnancy cohort, the mean rate of new tumor and peritumoral cyst development during the time when the women were pregnant (0.4 ± 0.4 tumors/year) did not differ significantly from the rate during the time when they were not pregnant (0.3 ± 0.4 tumors/year). The rate was also similar to that of the no-pregnancy cohort (0.3 ± 0.5 tumors/year). The annualized growth rate during pregnancy was 29.8% ± 42.7%, and the rate of growth for the same tumors during the time that the women were not pregnant was 41.4% ± 51.4%, which was not different from the growth rates in the no-pregnancy cohort. The rate of peritumoral cyst development was also similar in the pregnancy and no-pregnancy cohorts, but was higher during the nonpregnant periods in the pregnancy cohort. The need for surgery and the average age at surgery did not differ significantly between the pregnancy cohort (surgery required for 28% of hemangioblastomas, mean patient age at surgery 30.2 years) and no-pregnancy cohort (19%, 32.3 years).

This study provides new insight into the effect of pregnancy on hemangioblastomas but does have limitations. First, the sample size of the pregnancy cohort is small and may not be powered enough to detect small differences in growth rates. Also there is some inherent bias as patients self-select to become pregnant. Further, baseline differences in tumor characteristics (size, location, neurological impairment) may have limited those in the no-pregnancy cohort from becoming or attempting to become pregnant. The tumor volume was estimated utilizing an ellipsoid formula, but it is unclear if the measurements were verified to confirm accuracy. Furthermore, it is unclear if the measurements were performed in a blinded fashion by an independent reviewer. Curiously, peritumoral cyst growth rates were higher in the nonpregnant period in the pregnancy cohort compared to both the rate during pregnancy and the rate in the no-pregnancy cohort. This indicates a need for further investigation to determine what changes occur in the nonpregnant period that lead to cyst progression.

Nevertheless, Ye et al. should be commended for performing the first prospective study that directly addresses the effect of pregnancy on rates of tumor growth and progression as well as development of new tumors and peritumoral cysts by a direct comparison of radiological data obtained in a group of VHL disease patients during pregnancy and during times when these same individuals were not pregnant, as well as similar data obtained in patients who did not become pregnant during the study period. The internal control of the comparison of the pregnant and nonpregnant periods in the pregnancy cohort further emphasized the safety of pregnancy in these individuals. The findings directly challenge the notions that cyst progression and hemangioblastoma growth are accelerated during pregnancy. This study will provide guidance to both obstetricians and neurosurgeons when it comes to educating and managing patients with VHL disease who are or may become pregnant.

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Disclosure

The authors report no conflict of interest.

References

1. Depret-Mosser S, Jomin M, Monnier JC, Vinatier D, Bouthors-Ducloy AS, Christiaens JL, et al: [Cerebral tumors and pregnancy. Apropos of 8 cases.] **J Gynecol Obstet Biol Reprod (Paris) 22:**71– 80, 1993 (Fr)
2. Erdogan B, Sen O, Aydin MV, Bagis T, Bavbek M: Cerebellar hemangioblastoma in pregnancy. A case report. **J Reprod Med 47:**864–866, 2002
3. Gnarra J, Ward J, Porter F, Wagner J, Devor D, Grinberg A, et al: Defective placental vasculogenesis causes embryonic lethality in VHL-deficient mice. **Proc Natl Acad Sci U S A 94:**9102–9107, 1997
4. Grimbert P, Chauveau D, Remy SR, Grunfeld JP: Pregnancy in von Hippel-Lindau disease. **Am J Obstet Gynecol 180 (1 Pt 1):**110–111, 1999
5. Hayden MG, Gephart R, Kalanithi P, Chou D: Von Hippel-Lindau disease in pregnancy: a brief review. **J Clin Neurosci 16:**611–613, 2009
6. Huang JS, Huang CJ, Chen SK, Chien CC, Chen CW, Lin CM: Associations between VHL genotype and clinical phenotype in familial von Hippel-Lindau disease**. Eur J Clin Invest 37:** 492–500, 2007
7. Jagannathan J, Lonser RR, Smith R, DeVroom HL, Oldfield EH: Surgical management of cerebellar hemangioblastomas in patients with von Hippel-Lindau disease. **J Neurosurg 108:**210–222, 2008
8. Kasarskis EJ, Tibbs PA, Lee C: Cerebellar hemangioblastoma symptomatic during pregnancy. **Neurosurgery 22:**770-772, 1988
9. Nathan L, Satin AJ, Twickler DM: Cerebellar hemangioblastoma complicating pregnancy. A case report. **J Reprod Med 40:**662–664, 1995
10. Othmane IS, Shields C, Singh A, Shields J, Goldman W*:* Postpartum cerebellar herniation in von Hippel-Lindau syndrome. **Am J Ophthalmol 128:**387–389, 1999
11. Saegusa T, Ito K, Oba N, Matsuda M, Kojima K, Tohyama K, et al: Enlargement of multiple cavernous hemangiomas of the liver in association with pregnancy. **Intern Med 34:**207–11, 1995
12. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH: The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. **J Neurosurg 98:** 82–94, 2003
13. Ye DY, Bakhtian KD, Asthagiri AR, Lonser RR: Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. Clinical article. **J Neurosurg** [epub ahead of print August 31, 2012. DOI: 10.3171/2012.7.JNS12367]

Response

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We appreciate Dr. Shaw's and Dr. Chiocca's insightful comments regarding our study. Given the paucity of clinical evidence describing the effect of pregnancy on the development and progression of hemangioblastomas and associated cysts in patients with VHL disease, we sought to quantify the impact that pregnancy has on CNS hemangioblastoma progression and symptom development in this neoplastic disorder. Specifically, we prospectively analyzed and compared the development and progression of CNS hemangioblastomas and associated cysts (177 tumors, 28 cysts) in reproductive-age female patients with VHL disease who became pregnant (32 tumors, 5 cysts) versus the same such growth and development in a cohort of reproductive-aged female VHL disease patients who did not become pregnant (145 tumors, 23 cysts). Further, we analyzed for potential individual biological differences by comparing hemangioblastoma and cyst development and progression within the pregnancy cohort during the periods when the women were pregnant and the periods when they were not.

Whereas prior case reports suggested that pregnancy could alter development and progression of CNS hemangioblastomas and/or associated cysts,[1–9] this prospective long-term analysis (mean follow-up 7.5 ± 2.3 years) of serial clinical and MRI evaluations demonstrated no significant difference between the pregnancy and no-pregnancy cohorts with respect to the development or progression of hemangioblastomas and associated cysts. Moreover, in the pregnancy cohort, there was no significant difference in the development or progression of hemangioblastomas and associated cysts during the time when the women were pregnant compared with the time when they were not pregnant. Specifically, hemangioblastomas demonstrated similar growth during pregnancy (30% growth per year) compared to nonpregnant periods (41%) and to the tumors in the cohort of women who did not become pregnant (34%). Peritumoral cysts grew at similar rates in the no-pregnancy cohort (484%) and during pregnancy in the pregnancy cohort (571% per year). Finally, cyst growth was higher during nonpregnant periods in the pregnant cohort, which underscored the fact that pregnancy does not accelerate cyst progression.

Previous reports that suggested pregnancy enhances hemangioblastoma and/or cyst development or progres-