Gynecology and Reproductive Health Issues in von Hippel-Lindau disease

Pamela Stratton, MD
Christina Awad, Medical Student Year 4

Gynecology Consult Service
Program in Reproductive and Adult Endocrinology
Gynecology and Reproductive Health Issues Informed by Clinical Manifestations of von Hippel-Lindau Disease

- Autosomal dominant

- Tumors or fluid-filled sacs (cysts) occur
  - CNS: retinal hemangioblastomas, Central nervous system hemangioblastomas
  - Kidney: renal cysts or clear cell renal carcinoma
  - Pancreas: neuroendocrine tumor
  - Adrenal: pheochromocytoma
  - Inner Ear: endolymphatic sac tumors
  - Gynecology: Broad ligament cystadenomas; lipid cell tumors

- Serious or life-threatening complications
  - Hemangioblastomas
  - Renal Cancer
  - Pheochromocytoma during pregnancy
Familial von Hippel-Lindau Disease

- **Type 1** – low risk of pheochromocytoma
  - Retinal angioma, CNS hemangioblastoma, renal cell cancer, pancreatic cysts, and neuroendocrine tumors

- **Type 2** – high risk of pheochromocytoma
  - **Type 2A** – hemangioblastomas and pheochromocytoma
  - **Type 2B** – hemangioblastomas, pheochromocytoma and renal cell cancer
  - **Type 2C** – only pheochromocytoma

Kaelin Nat Rev Cancer 2002; Chen Hum Mol Genet 2001
Hes Hum Genet 2000; Zbar Hum Mutat 1996
Gynecology and Reproductive Health
Issues in von Hippel-Lindau Disease

- Reproductive health: Preconception decision to become pregnant
- Pregnancy and possible complications
- Imaging and surveillance for women during pregnancy
- Contraception
- Gynecological tumors
Reproductive Health in VHL: Preconception

- VHL not associated with infertility
- Discuss contraception if not interested in pregnancy (copper IUD may be an option)
- Genetic counseling and family history
- Determine of familial type of VHL disease
- Coordinated care with a multi-disciplinary team comprised of neurology, neurosurgery, ophthalmology, urology, radiology and anesthesiology
- Update screening imaging tests
- Discuss option of preimplantation genetic diagnosis to avoid having affected offspring

Adekola Obstet Gynecol Surv 2013
Reproductive Health in VHL: Preconception

- Decision to become pregnant based on maternal health and desire to have children

- Genetic counseling, family history, familial type of VHL disease, and individual’s current VHL disease impact timing of pregnancy

- Ideally, multi-disciplinary team assess and treat significant VHL disease – pheochromocytoma, symptomatic hemangioblastoma, and significant kidney cancer - prior to pregnancy

- Options to assess whether fetus affected
  - pre-implantation diagnosis as part of assisted reproduction
  - chorionic villus sampling
  - amniocentesis
  - neonatal testing

Adekola Obstet Gynecol Surv 2013
Reproductive Health in VHL: Pregnancy and possible VHL-related complications

- Risk of progression of hemangioblastomas
- Hemangioblastomas have been safely removed during pregnancy
- Hemangioblastomas may be affected by labor and pain
- Pheochromocytomas diagnosed during pregnancy pose risks to the mother and fetus
- Pheochromocytomas may need to be removed during pregnancy
- Kidney cancer risk to mother and fetus unknown
- What are options for pain control during labor?
- Is the route of delivery altered because of VHL-related CNS hemangioblastomas or pheochromocytoma?
- What are the risks of preterm birth?
Reproductive Health in VHL: Pregnancy and possible complications

- CNS hemangioblastomas
  - Is there risk of progression of hemangioblastomas during pregnancy?
  - How does labor and pain control during labor affect hemangioblastomas?
  - Is the route of delivery altered because of VHL-related CNS hemangioblastomas?

- Pheochromocytoma
  - How is pheochromocytoma diagnosed during pregnancy?
  - What happens if a pheochromocytoma is diagnosed during pregnancy?
Pregnancy in VHL patients: Does pregnancy cause progression of VHL disease?

- Case series of 30 women having 56 pregnancies
- Most patients remained asymptomatic
- 1 woman had VHL symptoms before pregnancy
- 3 women developed VHL symptoms during pregnancy
  - Raised intracranial pressure secondary to cerebellar hemangioblastoma
  - Malignant hypertension from pheochromocytoma
  - Acute abdomen arising from pancreatic cystadenoma
Prospective study addressing effect of pregnancy on rates of tumor growth in 36 women with 177 hemangioblastomas

Pregnant cohort – 9 patients
- Assessed both during pregnancy and when not pregnant

Nonpregnant cohort – 26 patients

Pregnancy was not associated with increased hemangioblastoma development or growth of existing hemangioblastomas
Pregnancy in VHL patients: Does pregnancy cause progression of VHL disease?

- Retrospective review of 29 patients having 48 pregnancies
- Progression score of cerebellar hemangioblastomas significantly changed between before and after pregnancy ($p=0.049$, $n=12$)
- VHL disease-related complications occurred in 8 (17% of all pregnancies)
- 1 fetal mortality related to maternal pheochromocytoma
- 4 women had life-threatening situation
  - Hydrocephalus due to cerebellar hemangioblastoma ($n=2$)
  - Pheochromocytoma ($n=2$)

Conclusion
- Pregnancy induces cerebellar hemangioblastoma progression
- Pregnancy has a high VHL disease-related complication rate
Pheochromocytoma

http://endocrinology.org/adrenal/pheochromocytoma_diagnosis.shtml

http://www.ultrasound-images.com/adrenals.htm
Pheochromocytoma in Pregnant VHL patients

- Rare catecholamine-secreting tumor

- Symptoms:
  - Paroxysmal hypertension
  - Essential hypertension
  - Classic triad – episodic headaches, palpitations, and diaphoresis

- Diagnosis
  - Detection of elevated levels of catecholamines and their metabolites in urine
  - During pregnancy, tumor localized by MRI or ultrasound
Pheochromocytoma in Pregnant VHL patients

- May be overlooked during pregnancy because symptoms resemble
  - preeclampsia OR
  - other causes of hypertension like thyroid problems, cocaine use, cerebral hemorrhage or malignant hyperthermia

- Patients with type 2 VHL disease and intact adrenals may be offered biweekly non-stress testing and biophysical profiles from 28 weeks gestation given their potential risk of pheochromocytoma

Frantzen Neurology 2012
Pheochromocytoma in Pregnant VHL patients

- Maternal mortality in undiagnosed patients is higher than those diagnosed prenatally (14 to 25% versus 2 to 4%)
- Maternal and fetal complications arise in context of inadequate control of hypertension
- Hypertension is treated with various medications
- Ultimate treatment is surgery
  - Pheochromocytomas have been safely removed during pregnancy
- Potential problems during continued pregnancy or during delivery if pheochromocytoma is present
  - No specific recommendations on the mode or optimal timing of delivery
Approach to Prenatal Care in VHL patients: Obstetrical Anesthesia

- No specific recommendation

- Theoretical risk of rupturing a spinal hemangioblastoma or complications arising from increased intracranial pressure with use of epidural or spinal anesthesia

- Few case reports of successful epidural anesthesia

- Very few case reports of spinal anesthesia
  - McCarthy 2010

- General anesthesia is considered in emergency cases
Approach to Prenatal Care in VHL patients: Obstetrical Anesthesia

- Preferred to have spinal imaging prior to using epidural anesthesia
  - Location of CNS hemangioblastomas
  - Occurrence of cerebellar hemangioblastoma
  - Most spinal cord hemangioblastomas are cervical or thoracic; few are lumbar

- Epidural anesthesia may be indicated because of complications – autonomic dysreflexia following a spinal hemangioblastoma-induced paraplegia

- Successful adrenalectomies done under epidural anesthesia for pregnancies complicated by pheochromocytoma

Adekola Obstet Gynecol Surv 2013
Approach to Prenatal Care in VHL patients

- Every patient should be managed individually based on disease-related symptoms and signs - before and during pregnancy AND findings on imaging

- In patients with type 2 VHL, assess for pheochromocytoma during pregnancy

- Monitoring known hemangioblastomas and if change in symptoms, assess for new or change in existing hemangioblastomas

- Symptomatic VHL may be complicated by preterm delivery
  - 3 patients with VHL disease all delivered between 32 and 34 weeks
  - 7 patients undergoing cranial surgery during pregnancy; all but one had a term uneventful delivery

Grimbert Am J Obstet Gynecol 1999
Kasarkis Neurosurgery 1988

Adekola Obstet Gynecol Surg 2013
Approach to Prenatal Care in VHL patients

- On beginning prenatal care,
  - Obtain detailed history of VHL disease
  - Review imaging studies
  - Update imaging within the parameters of safe assessment in pregnancy
    - MRI or ultrasound are preferred

- Care team includes
  - Genetic counselor
  - Maternal-fetal-medicine specialist
  - Neurology, neurosurgery, ophthalmology, urology, radiology and anesthesiology
Management of VHL in Pregnancy: During Pregnancy

- Genetic counseling, family history and determine familial type of VHL disease if unknown
- Offer prenatal diagnostic testing to determine whether fetus is affected
- Update screening imaging tests if not up-to-date
  - Intensified surveillance for cerebellar hemangioblastoma and pheochromocytoma during preconception and pregnancy
  - MRI without contrast of the cerebellum at four months’ gestation
- Multidisciplinary care including maternal-fetal-medicine specialist, neurology, neurosurgery, ophthalmology, urology, radiology and anesthesiology
- Mode of delivery and anesthesia determined by multidisciplinary team in conjunction with patient
Management of VHL in Pregnancy: Intrapartum

- Vaginal delivery may be attempted in the absence of symptomatic intracranial tumor.
- In the presence of an asymptomatic intracranial tumor, 2nd stage of labor may be shortened by operative vaginal delivery.
- In the absence of symptomatic intracranial tumor and lumbosacral spinal hemangioblastoma, epidural anesthesia may be used for pain control.
- Cesarean delivery may be indicated as part of life-preserving VHL disease-related surgical management.

Adekola Obstet Gynecol Surv 2013
Management of VHL in Pregnancy: Postpartum

- Neurological assessment
  - postpartum new occurrence or exacerbation of CNS symptoms
  - symptoms include: limb spasticity, worsening gait, shortness of breath and severe headaches, ocular papilledema, cerebellar pontine herniation, weakness and sensory loss after parturition

- Breastfeeding is not contraindicated

- Avoid hormonal contraception especially high dose progestins based on theoretical risk of hemangioblastoma growth

- Nonhormonal long-acting reversible contraception (copper IUD) is a reasonable choice

- Follow-up with multidisciplinary care neurology, neurosurgery, ophthalmology, urology, and radiology
Gynecology and Reproductive Health Issues: Contraception in VHL patients

- Planned pregnancy in VHL is associated with the best maternal and fetal outcomes.
- Considerations regarding type of contraception.
- Long acting methods are associated with the lowest pregnancy rates. Examples include:
  - Depo provera
  - Progestin implants
  - Progestin or copper IUD
Gynecology and Reproductive Health

Issues: Contraception in VHL patients

- Hemangioblastomas may have progesterone receptors and thus may be stimulated by use of progestin containing contraception especially high dose progestins
- Avoid depo provera or progestin implants (Implanon)
- A copper IUD is the only nonhormonal long acting contraceptive
- Progestin IUD has low dose progestin and may be considered
Reproductive tract tumors

- Papillary cystadenomas of the broad ligament
- Lipid cell tumors of ovary
- Bilateral ovarian serous cystadenomas
Papillary cystadenoma of the Broad Ligament in VHL

- Often incidental finding in the mesosalpinx and broad ligament; 12 cases reported to date
- Arising in remnants of mesonephric ducts
- Surgery warranted to exclude possibility of metastatic renal cancer

Clear cell papillary cystadenoma (CCPC) and endometrioid cystadenofibroma are present in the mesosalpinx
Lipid Cell Tumor in Women with VHL

- Two patients in their late 20s presented with symptoms: amenorrhea, hirsutism, clitoromegaly and complex adnexal masses

- Hormonal assessment showed both secreted testosterone

Wagner Obstet Gynecol 2010
Gynecology and Reproductive Health Issues in von Hippel-Lindau Disease

- Reproductive health: Preconception decision to become pregnant
- Pregnancy complications related to hemangioblastomas or pheochromocytomas
  - Intensified surveillance for cerebellar hemangioblastoma and pheochromocytoma during preconception and pregnancy
  - MRI without contrast of the cerebellum at four months’ gestation
- Contraception – nonhormonal long acting methods
- Gynecological tumors – rare
  - Consider if pelvic mass or virilization
Acknowledgments

- Dr. Marston Linehan
- Staff of the urologic oncology branch
- Patients with VHL